

Enantioselective Alkylation of Glycine Imines Using a Cinchona-Functionalized Crown Ether-Strapped Calixarene Phase-Transfer Catalyst

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5.1 Introduction

The formation of a new carbon–carbon bond alpha (α) to a carbonyl group is one of the most important reactions in organic synthesis and has contributed significantly to the development of organic chemistry as a whole. In this respect, esters have found widespread use. Undoubtedly this is due to the diversity of esters derived enolate chemistry and the abundance of α -substituted esters (and derivatives) in biologically active systems. Phase-transfer alkylation using a chiral catalyst and a prochiral protected glycine derivative is a particularly attractive method for the preparation of optically active α -alkyl- α -amino acids. Asymmetric phase-transfer alkylation of a prochiral glycine derivative can be achieved by using chiral phase-transfer catalysts derived from relatively cheap, commercially available cinchona alkaloids, the only drawback of this approach is the moderate enantioselectivity of α -alkyl- α -amino acid products. The use of chiral phase transfer catalysts for asymmetric alkylation of glycine esters was first reported by O'Donnel(O'Donnell et al., 1989).In this alkylation N-benzyl derivatives of chinchona alkaloids were used also the salts derived from cinchonine and cinchonidine gave rise to higher levels of enantioselectivity(Lygo and Wainwright, 1997, Lygo et al., 2001)

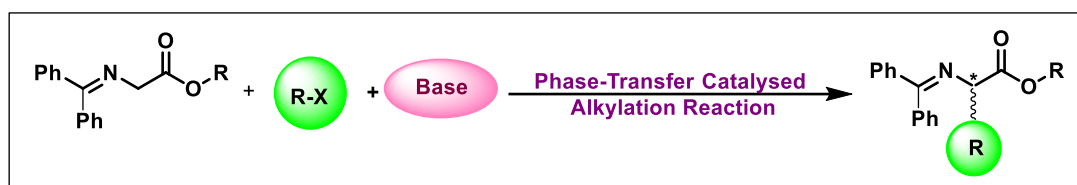


Figure 5.1 General scheme for phase transfer catalysed asymmetric alkylation reaction

5.1.1 Earlier work

In 1984, the first efficient chiral phase-transfer catalyst, *N*-(*p*-(trifluoromethyl)benzyl)cinchonidium bromide, was devised by the Merck group for asymmetric methylation of 6,7-dichloro-5-methoxy-2-phenyl-1-indanone, giving 92% ee(Dolling et al., 1984).After 5 years of this successful endeavor, similar *N*-(benzyl)cinchonidium chloride has been applied by O'Donnell to asymmetric alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester(O'Donnell et al., 1989). Lygo designed *N*-anthracenylmethylammonium salts and utilised in asymmetric alkylation of a benzophenone-derived glycine-imine, and carried out enantioselective synthesis of a range of α -amino acid esters (e.e. 67–94%)(Lygo and Wainwright, 1997). Corey prepared *O*-allyl-*N*-anthracenylmethyl cinchonidium salt(Corey et al., 1997).Jew prepared several dimeric ammonium salts from cinchonidine and α,α' -dibromo-*o*-xylene, α,α' -dibromo-*m*-xylene, and α,α' -dibromo-*p*-xylene the catalytic enantioselective alkylation of *N*-(diphenylmethylene) glycine *tert*-butyl ester in a high enantiomeric excess (90–99% ee) (Jew et al., 2001). Jew further developed this strategy to synthesize triply oriented cinchona alkaloid-derived chiral phase-transfer catalyst from α,α',α'' -tribromomesitylene and 3 equiv of cinchonidine(Park et al., 2001). Jew later showed catalytic efficiency of cinchona alkaloid PTC with Najera also prepared new dimeric cinchonidine- and cinchonine-derived ammonium salts which incorporate a dimethylantracenyl bridge as a spacer.(Chinchilla et al., 2002). Cahard and Plaquevent greatly improved the stereoselectivity by attaching Merrifield resin on the hydroxy moiety of cinchonidine derivative(Thierry et al., 2001).

The only reported examples pertaining to calixarene-functionalized phase-transfer α -alkylation of glycine imine (figure 5.2) are reported by Sirit (57% ee) (Bozkurt et al., 2008) and Neri (47% ee) (De Simone et al., 2017a) and an unconfirmed report with good enantioselectivity (91% ee). (Huang et al., 2012)

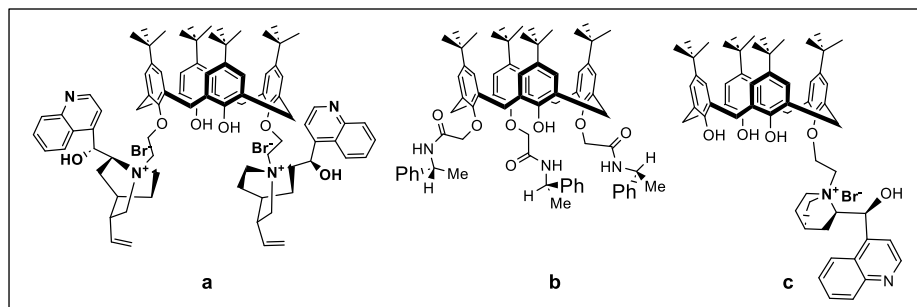


Figure 5.2 Represents catalyst prepared by (a) Sirit; (b) Neri; (c) Huang

5.1.2 Our work

A newly designed quaternary ammonium *Cinchona*-functionalized crown ether-strapped calix[4]arenes as PTCs (**C3** and **C4**) for asymmetric α -alkylation of glycine imines to α -alkylated glycines with remarkable selectivity under ambient conditions *Cinchona* cationic moiety of the catalyst transfers chirality to the substrate through noncovalent interactions and π - π stacking, and the crown ether pendulum enhances enantioselectivities and the rate of reaction by generating a chiral ion pair via Na^+ ion binding, a pivotal step in the phase-transfer catalysis.

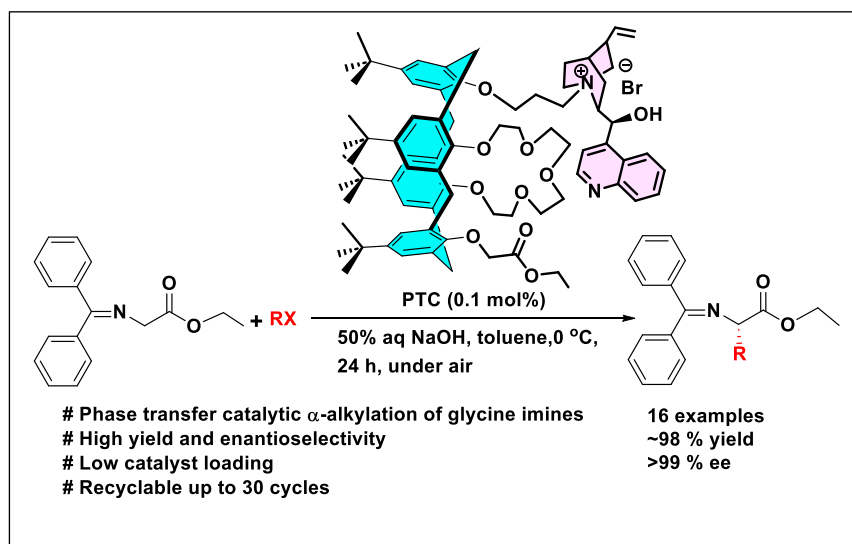


Figure 5.3 Phase transfer catalysed asymmetric alkylation reaction of N-(diphenylmethylene) glycine ethyl ester

5.2 Experimental Section

General Remarks

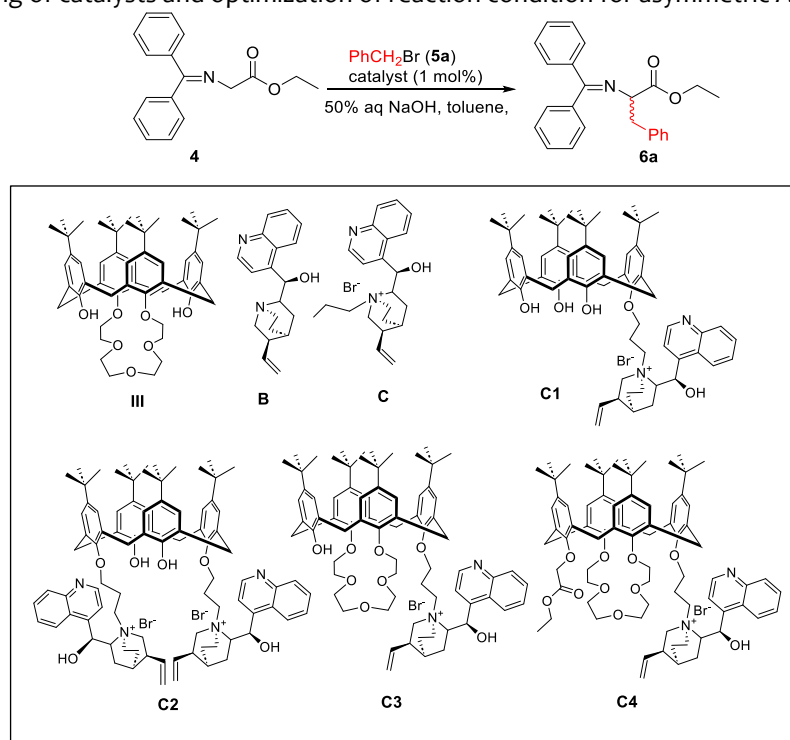
A 10 ml round bottom flask was charged with N-(diphenylmethylene) glycine ethyl ester **4** (26.7 mg, 0.1 mmol), NaOH (0.6 mL), and catalyst-C4 (0.13 mg, 0.1 mol%), then alkylating agent **5a** (21 mg, 15 μL , 0.12 mmol) in toluene (1 mL) was added. The reaction mixture was stirred at 0 $^{\circ}\text{C}$ (using Julabo FT903 - Immersion Cooler) for 24 h and monitored by TLC. The enantiomeric excess (ee) of the alkylation products were determined by HPLC measurements carried out using a Waters Model 2489 equipped with chiral columns DAICEL 4.6 mm $\times$ 250 mm Chiralpak- OD-

H and AD-H using condition n- Hexane/isopropanol solvent system. High resolution mass spectra (HRMS) were acquired using an Agilent technologies model G6564 QTOF. The samples were ionized in positive ion mode using a MALDI or ESI ionization sources.

5.2.1 Enantioselective Alkylation of Glycine Imines and effect of catalysts

Our studies started with an examination of asymmetric α -alkylation of model substrate *N*-(diphenylmethylene) glycine ethyl ester **4a** with benzyl bromide **5a** to form optically active *N*-(diphenylmethylene) phenylalanine ethyl ester **6a**. Initially, the catalysts **I–C7** were tested at 1 mol % catalyst loading in toluene table 5.1 using 50% aq NaOH at RT to afford the desired α -benzylated product **6a**. The yield and enantioselectivity were ameliorated with cinchonidine-appended calix[4]arene-strapped crown ether (**C3**) (entry 6) in 24 h. To our surprise, high yield and enantioselectivity were afforded in a shorter reaction time with sterically directed catalyst **C4** (entry 7). Other solvents gave moderate to good conversions but low enantioselectivities (entries 8–15) after a longer reaction time. The reaction conditions were further optimized by lowering the reaction temperature to $-10\text{ }^{\circ}\text{C}$ (entries 16–20) using catalyst **C4**. The reaction worked smoothly when the temperature was reduced to 10 and $5\text{ }^{\circ}\text{C}$ with comparable yield and selectivity (entries 16 and 17, respectively). At $0\text{ }^{\circ}\text{C}$, a high yield ($\sim 98\%$) and enantioselectivity ($>99\%$ ee) were obtained in 24 h (entry 18). Further decreasing of temperature to -5 and $-10\text{ }^{\circ}\text{C}$ resulted in poor conversion due to the poor solubility of the catalyst (entries 19 and 20, respectively). Lowering the catalyst loading improved the selectivity to 99.2% ee (entry 21; 0.5 mol % catalyst) and 99.9% ee (entry 22; 0.1 mol % catalyst), indicating the kinetic control nature of the reaction. Further reduction of catalyst loading has a negative impact on the yield and selectivity (entry 23). Additionally, NaOH was found to be the most optimal base in terms of yield and enantioselectivity due to favorable recognition of Na^+ with calix-[5]-crown (Table 5.2).

Table 5.1. Screening of catalysts and optimization of reaction condition for asymmetric Alkylation reaction ^a



Entry	Catalyst	Solvent	Time ^b (h)	Temp (° C)	% Yield ^c	%ee ^d (Config.)
1	III	Toluene	48	25	<20	n.d.
2	B	Toluene	48	25	55	32 (S)
3	C	Toluene	48	25	60	41 (S)
4	C1	Toluene	48	25	68	45 (S)
5	C2	Toluene	48	25	65	42 (S)
6	C3	Toluene	24	25	92	69 (S)
7	C4	Toluene	12	25	98	80 (S)
8	C4	DMF	48	25	20	33 (S)
9	C4	DMSO	48	25	25	42 (S)
10	C4	HMPA	48	25	32	38 (S)
11	C4	CH ₃ CN	48	25	16	18 (S)
12	C4	CHCl ₃	48	25	67	22 (S)
13	C4	CH ₂ Cl ₂	48	25	71	28 (S)
14	C4	Ether	72	25	<5	n.d.
15	C4	THF	72	25	<10	n.d.
16	C4	Toluene	15	10	97	88 (S)
17	C4	Toluene	18	5	96	92 (S)
18	C4	Toluene	24	0	98	99.1 (S)
19	C4	Toluene	36	-5	65	89 (S)
20	C4	Toluene	72	-10	42	81 (S)
21 ^e	C4	Toluene	24	0	98	99.2 (S)
22 ^f	C4	Toluene	24	0	98	99.9 (S)
23 ^g	C4	Toluene	45	0	92	91 (S)

^aUnless otherwise stated, the reaction was carried at room temperature in 1 mL toluene with 0.1 mmol **4**, 0.12 mmol **5a**, 1.0 mol % catalyst, and 50% aq NaOH (0.6 mL). ^bBased on TLC analysis of N-(diphenylmethylene) glycine ethyl ester **4** consumption. ^cIsolated yields. ^dDetermined by HPLC equipped with Daicel Chiralpak OD-H column. ^eCatalyst (0.5 mol%), ^fCatalyst (0.1 mol%) and ^gCatalyst (0.05 mol%).

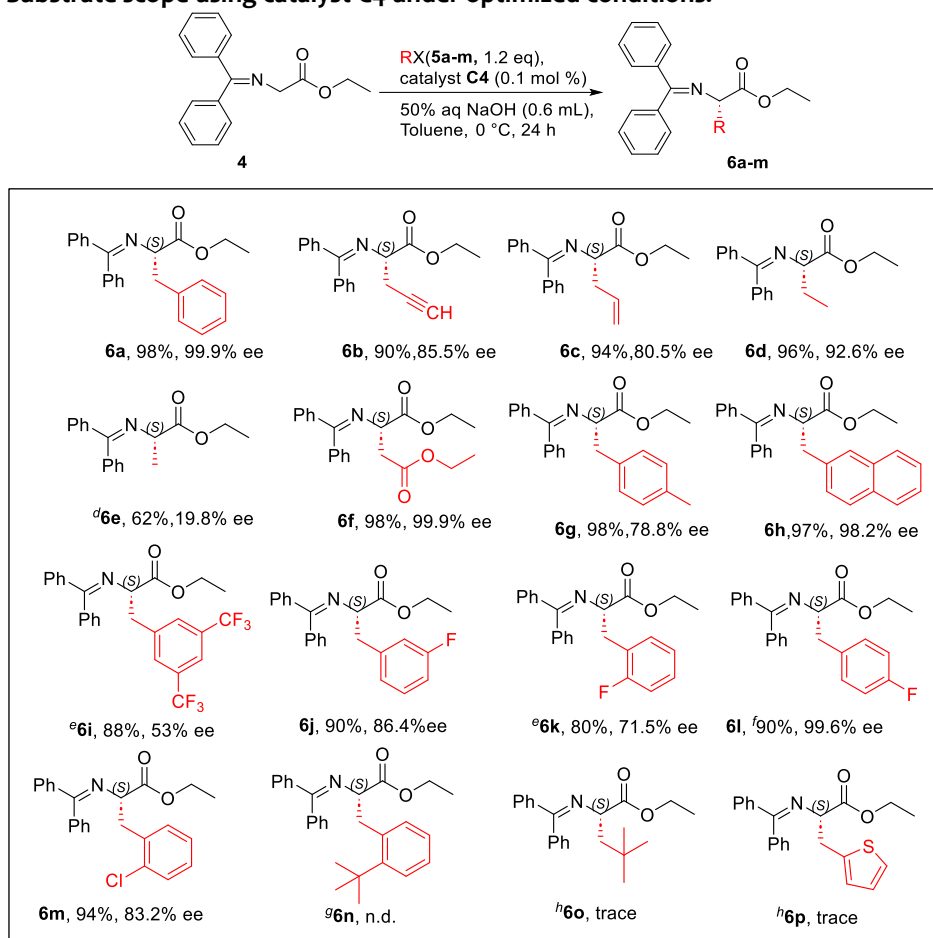
Thus, the optimal reaction conditions were found to be 0.1 mmol N-(diphenylmethylene) glycine ethyl ester **4** and 0.12 mmol alkylating agent **5a** in 50% NaOH (0.6 ml) with 0.1 mol % catalyst loading at 0 °C for 24 h. The optimized reaction conditions using catalyst **C4** have broad applicability toward the asymmetric alkylation of **4** with different alkyl halides as shown in Scheme 5.1. Very good yields and enantiomeric excess (ee) were realized with aryl-, alkyl-, and fluoro-substituted benzyl bromides (**6a-d** and **6g-l**). When propargyl, allyl, and ethyl bromide were used, the corresponding α -alkylated glycinate esters were obtained in high yields and enantioselectivities (**6b-d**, respectively). However, poor enantioselectivity was obtained with less active methyl iodide at a higher (5 mol %) catalytic loading (**6e**, 19.8% ee). Surprisingly, electron-rich ethyl bromoacetate gave exceptional enantioselectivity (99.9% ee) due to favorable interactions of the polar ester group with the substrate and catalyst (**6f**). While a benzyl bromide substitute with electron donating *p*-CH₃- underwent smooth conversion for **6g**, high conversion (97%) and selectivity (>98% ee) were realized for the 1-naphthyl methyl group (**6h**). Fluorinated benzyl bromides gave high yields and enantioselectivities due to the strong noncovalent interaction of the fluorine atom (**6j-l**) with the catalyst and glycinate ester except in **6i**, where a steric factor dominated that led to low enantioselectivity after 48 h. Unexpectedly, *p*-fluoro benzyl bromide reacted very fast with a 90% yield and 99.6% ee in 10 h compared to *ortho* and *meta* substituents. A similar tendency was observed for chloro-substituted benzyl bromide (**6m**; 94%, 83% ee). Our attempts to synthesize α -alkylated glycinate esters with large groups, such as 2-*tert*-butylbenzyl and neopentyl, were unsuccessful due to steric inhibition of the *tert*-butyl moiety (**6n** and **6o**). With 2-thienyl bromide, the desired alkylated glycinate was rarely obtained (**6p**).

Table 5.2 Screening of base

Entry	Base	Time (h) ^a	Yield (%) ^b	ee (%) ^c
1	n.a	72	-	-
2	CsF	24	51	36 (S)
3	Cs ₂ CO ₃	24	45	40 (S)
4	Na ₂ CO ₃	24	60	30 (S)
5	K ₂ CO ₃	24	62	35 (S)
6	NaOH	24	98	80 (S)
7	KOH	24	94	62 (S)
8	CsOH	24	60	30 (S)

^aDetermined by monitoring the consumption of N-(diphenylmethylene)glycine ethyl ester **4** by TLC. ^bIsolated yield. ^cDetermined by HPLC equipped with Daicel Chiralpak OD-H.

Scheme 5.1: Substrate scope using catalyst **C4** under optimized conditions.^{a,b,c}



^aReaction conditions: **4** (0.1 mmol), **5** (0.12 mmol), catalyst **C4** (0.1 mol%), 50% aq NaOH (0.6 mL), toluene (1 mL), 0 °C, 24 h, under air. ^bIsolated yield, rest starting materials. ^c% ee determined by HPLC equipped with chiral columns and configuration was determined by relative retention time and specific rotation with literature data; See Supporting Information for details. ^d5 mol% catalyst loading. ^eReaction time 48 h. ^fReaction completed in 10 h. ^g10 mol% catalytic loading, 72 h. ^h5 mol% catalytic loading, 48 h.

5.3 Recyclability of catalysts

The catalyst **C4** is abysmally soluble in diethyl ether at room temperature as it shows selective solubility profile shown in table 5.1 Therefore, it could be easily recovered by simply dissolving alkylated glycinate and recycled without compromising catalytic activity

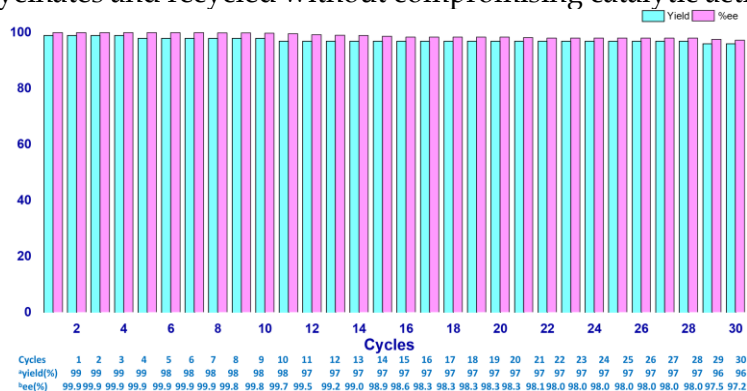
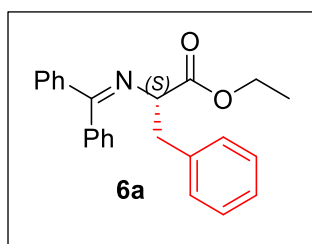


Figure 5.4. Recyclability test of catalyst **C4** for **6a**. Reaction conditions are as follows: **4** (10 mmol), **5a** (12 mmol), 50% aq NaOH (60 mL), and catalyst **C4** (0.1 mol %) in toluene (100 mL) at 0 °C for 24 h under air. ^aIsolated yield. ^b% ee was determined by HPLC equipped with a Daicel Chiralpak OD-H column

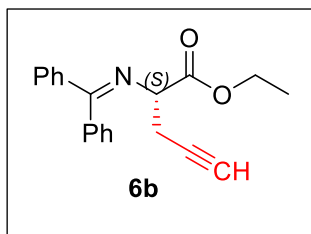
5.4 Conclusion

We reported two efficient new chiral PTCs derived from quaternary ammonium *Cinchona* functionalized crown-ether-strapped calix[4]arene (**C3** and **C4**). The catalytic activity was investigated for asymmetric α -alkylation of glycine imines, and sterically directed catalyst **C4** demonstrated excellent activity for diverse alkylating groups to give α -alkylated glycinate (up to ~98% yield and 99.9% ee) at 0.1 mol% catalytic loading. Importantly, the catalyst was readily recoverable and recycled up to 30 test cycles at gram scale without noticeable drop in catalytic reactivity.

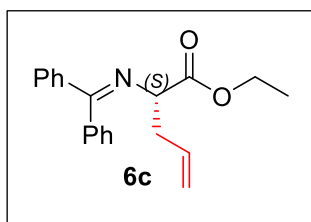
5.5 Product Analysis



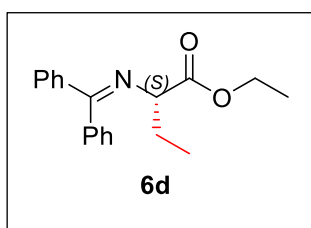
Ethyl 2-((diphenylmethylene)amino)-3-phenylpropanoate (6a): Colorless oil, 35.01 mg, 98% yield. Silica gel (petroleum ether–ethyl acetate: 98:2 to 90:10) afforded the pure alkylated product. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak OD-H, hexane/2-propanol = 0.45/0.05, flow rate = 0.5 mL/min, wavelength = 210 nm, retention time; 9.0 min (major) and 12.0 min (minor): $[\alpha]^{28}_D = -20.8^\circ$ ($c = 1.0$, CHCl_3 ; 99.9% ee); ^1H NMR (500 MHz, CHloroform-d) δ 7.60–7.58 (m, 4H), 7.51 (s, 3H), 7.43 (dd, $J = 7.9, 1.8$ Hz, 5H), 7.30 (d, $J = 4.9$ Hz, 2H), 7.27 (d, $J = 1.3$ Hz, 2H), 4.15–4.09 (m, 1H), 4.09–4.02 (m, 2H), 3.42 (dt, $J = 6.4, 1.8$ Hz, 2H), 1.07 (td, $J = 7.2, 1.3$ Hz, 3H). ^{13}C NMR (126 MHz, CHloroform-d) δ 171.8, 170.6, 139.3, 137.6, 136.36, 130.0, 129.3, 128.2, 128.0, 128.0, 127.8, 126.5, 64.4, 61.6, 37.1, 14.1. HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{23}\text{NO}_2$ 357.1729, found 357.1728



Ethyl 2-((diphenylmethylene)amino) pent-4-ynoate (6b): Light yellow oil; 27.48 mg, 90% yield). Silica gel (petroleum ether–ethyl acetate: 98:2 to 90:10) afforded the pure alkylated product. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak OD-H, hexane/2-propanol = 0.45/0.05, flow rate = 0.5 mL/min, wavelength = 210 nm, retention time; 15.5 min (major) and 19.0 min (minor): $[\alpha]_{\text{D}}^{28} = -30.4^\circ$ ($c = 1.0$, CHCl_3 ; 85.5% ee); ^1H NMR (500 MHz, Chloroform- d) δ 7.67 – 7.60 (m, 2H), 7.45– 7.40 (m, 3H), 7.40 (tt, $J = 7.4$ Hz, 1H), 7.35 (tt, $J = 1.3, 8.3, 6.7$ Hz, 2H), 7.34 – 7.32 (m, 2H), 4.30 (dd, $J = 8.2, 5.1$ Hz, 1H), 4.29 – 4.14 (m, 2H), 2.88 – 2.76 (m, 2H), 1.95 (t, $J = 2.7$ Hz, 1H), 1.29 – 1.27 (t, $J = 7.2$ Hz, 3H).; ^{13}C NMR (126 MHz, Chloroform- d) δ 170.6, 132.5, 130.1, 128.5, 128.3, 128.1, 81.0, 70.3, 70.3, 64.1, 61.4, 37.2, 32.0, 29.8, 29.8, 27.1, 22.8, 14.2, 14.2. HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_2$ 306.1416, found 306.1415

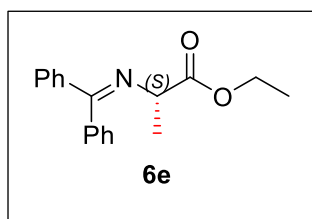


Ethyl 2-((diphenylmethylene)amino) pent-4-enoate (6c): Colorless oil, 28.89 mg, 94% yield. Silica gel (petroleum ether–ethyl acetate: 98:2 to 90:10) afforded the pure alkylated product. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak OD-H, hexane/2-propanol = 0.45/0.05, flow rate = 0.3 mL/min, wavelength = 210 nm, retention time; 16.0 min (major) and 21.1 min (minor): $[\alpha]_{\text{D}}^{28} = -10.2^\circ$ ($c = 1.0$, CHCl_3 ; 80.5% ee); ^1H NMR (500 MHz, Chloroform- d) δ 7.82 – 7.80 (m, 2H), 7.65 – 7.62 (m, 2H), 7.58 – 7.49 (m, 3H), 7.47– 7.32 (m, 1H), 7.32– 7.30 (m, 3H), 5.69 – 5.66 (m, 1H), 5.08 – 5.00 (m, 2H), 4.21 – 4.20 (m, 2H), 4.15 – 4.12 (dd, $J = 5.8, 10$ Hz, 1H), 2.69 – 2.63 (m, 2H), 1.29 – 1.27 (m, 3H). ^{13}C NMR (126 MHz, Chloroform- d) δ 171.8, 170.6, 170.5, 139.6, 137.6, 136.4, 134.4, 132.4, 130.3, 130.0, 128.2, 128.0, 127.9, 117.5, 65.3, 60.9, 60.8, 55.7, 38.1, 29.7, 14.2, 14.2. HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{22}\text{NO}_2$ 308.1572, found 308.1571.

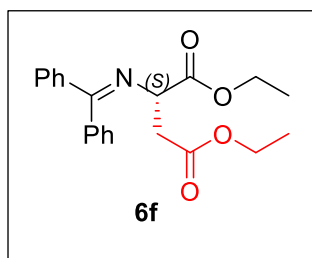


Ethyl 2-((diphenylmethylene)amino) butanoate (6d): Colorless oil, 28.35 mg, 96% yield. Silica gel (petroleum ether–ethyl acetate: 98:2 to 90:10) afforded the pure alkylated product. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak OD-H, hexane/2-propanol = 0.40/0.10, flow rate = 0.5 mL/min, wavelength = 210 nm, retention time; 13.8 min (major) and 15.2 min (minor): $[\alpha]_{\text{D}}^{28} = -32.4^\circ$ ($c = 1.0$, CHCl_3 ; 92.6% ee); ^1H NMR (500 MHz, Chloroform- d) δ 7.82–7.80 (dd, $J = 36.2, 7.6$ Hz, 1H), 7.67 – 7.50 (m, 2H), 7.49 – 7.44 (m, 3H), 7.40 – 7.32 (m, 2H), 7.20 – 6.87 (m, 2H), 4.23 – 4.18 (m, 3H), 1.61 – 1.54 (m, 2H), 1.29 – 1.26 (m, 6H). ^{13}C NMR (126 MHz, Chloroform- d) δ 171.9, 170.6, 139.2, 136.0, 132.4, 128.8, 128.7, 128.7, 128.2, 128.0,

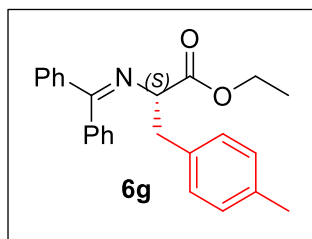
127.6, 60.8, 55.7, 31.6, 31.0, 29.7, 14.2. HRMS (ESI) m/z $[M]^+$ calcd for $C_{19}H_{21}NO_2$ 295.1572, found 295.1573.



Ethyl 2-((diphenylmethylene)amino) propanoate (6e): Colorless oil 17.44 mg, 62% yield. Silica gel (petroleum ether–ethyl acetate: 98:2 to 90:10) afforded the pure alkylated product. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol = 0.48/0.02, flow rate = 0.7 mL/min, 35 °C, wavelength = 210 nm, retention time; 17.7 min (major) and 21.0 min (minor): $[\alpha]^{28}_D = -28.9^\circ$ ($c = 1.0$, $CHCl_3$; 19.8% ee); ^1H NMR (500 MHz, Chloroform- d) δ 7.82–7.80 (m, 2H), 7.67–7.65 (m, 1H), 7.61–7.59 (m, 1H), 7.50–7.45 (t, $J = 7.4$ Hz, 4H), 7.45–7.40 (d, 2H), 7.20–7.18 (m, 1H), 4.27–4.11 (m, 3H), 1.42 (d, $J = 6.5$ Hz, 3H), 1.01 (t, $J = 5.5$ Hz, 3H). ^{13}C NMR (126 MHz, Chloroform- d) δ 171.9, 169.7, 137.6, 136.0, 132.4, 130.0, 128.2, 60.8, 60.8, 55.7, 19.1, 14.2. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{18}H_{19}NO_2$ 281.1416, found 281.1417.

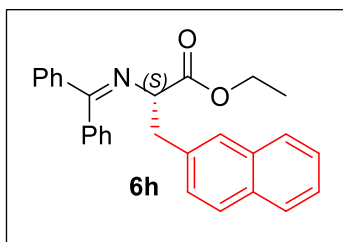


Diethyl 2-((diphenylmethylene)amino) succinate(6f): Colorless oil 34.63 mg, 98% yield. Silica gel (petroleum ether–ethyl acetate: 98:2 to 90:10) afforded the pure alkylated product. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak OD-H, hexane/2-propanol = 0.46/0.04, flow rate = 0.3 mL/min, wavelength = 210 nm, retention time; 17.2 min (major) and 19.5 min (minor): $[\alpha]^{28}_D = -35.4^\circ$ ($c = 1.0$, $CHCl_3$; 99.9% ee); ^1H NMR (500 MHz, Chloroform- d) δ 7.82–7.80 (m, 1H), 7.64–7.60 (m, 1H), 7.59–7.56 (m, 2H), 7.54–7.50 (m, 1H), 7.46 (dd, $J = 5.5, 2.0$ Hz, 3H), 7.40 (d, $J = 7.0$ Hz, 2H), 7.33 (t, $J = 7.6$ Hz, 2H), 4.31 (t, $J = 6.6$ Hz, 1H), 4.23–4.18 (m, 2H), 4.11–4.08 (m, 2H), 3.09–3.04 (m, 2H), 1.29–1.26 (m, 3H), 1.21 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (126 MHz, Chloroform- d) δ 170.9, 170.4, 137.6, 132.4, 130.0, 128.2, 63.0, 60.5, 37.1, 14.1, 14.1. HRMS (ESI) m/z $[M]^+$ calcd for $C_{21}H_{23}NO_4$ 353.1627, found 353.1628.

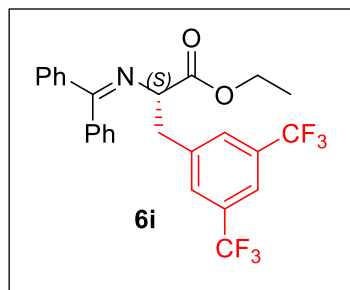


Ethyl 2-((diphenylmethylene)amino)-3-(p-tolyl)propanoate(6g): Yellow oil, 36.40 mg, 98% yield. Silica gel (petroleum ether–ethyl acetate: 98:2 to 90:10) afforded the pure alkylated product. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak OD-H, hexane/2-propanol = 0.42/0.08, flow rate = 0.6 mL/min, wavelength = 210 nm, retention time; 19.5 min (major) and 20.6 min (minor): $[\alpha]^{28}_D = -110.3^\circ$ ($c = 1.0$, $CHCl_3$; 78.8% ee); ^1H NMR (500 MHz,

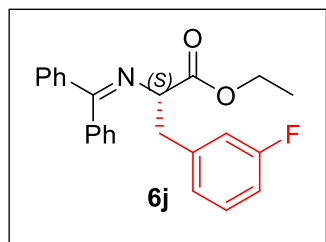
Chloroform-d) δ 7.58 (d, J = 7.4 Hz, 2H), 7.49 (t, J = 7.7 Hz, 3H), 7.47 – 7.33 (m, 2H), 7.29 – 7.26 (m, 3H), 6.99 (m, 4H), 4.20 (dd, J = 8.2, 7.0 Hz, 2H), 4.17 – 4.11 (m, 1H), 3.23 (dd, J = 13.4, 4.4 Hz, 1H), 3.12 (dd, J = 13.4, 9.2 Hz, 1H), 2.28 (s, 3H), 1.46 – 1.35 (m, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 171.8, 139.3, 137.6, 136.3, 135.8, 134.5, 132.4, 130.0, 129.32, 128.2, 128.0, 127.7, 126.5, 126.4, 64.4, 31.9, 14.1. HRMS (ESI) m/z $[M]^+$ calcd for $\text{C}_{25}\text{H}_{25}\text{NO}_2$ 371.1885, found 371.1886



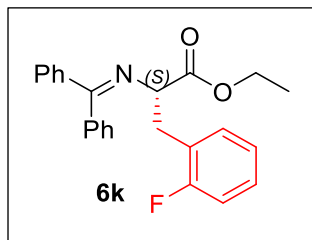
Ethyl 2-((diphenylmethylene)amino)-3-(naphthalen-2-yl)propanoate (6h): Colorless oil, 39.49 mg, 97% yield. Silica gel (petroleum ether–ethyl acetate: 98:2 to 90:10) afforded the pure alkylated product. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol = 0.46/0.04, flow rate = 0.7 mL/min, wavelength = 210 nm, retention time; 16.8 min (major) and 20.2 min (minor): $[\alpha]_{\text{D}}^{28} = -60.20$ (c = 1.0, CHCl_3 ; 98.2% ee); ^1H NMR (500 MHz, Chloroform-d) δ 7.82 – 7.79 (m, 7H), 7.62 – 7.57 (m, 3H), 7.49 (dd, J = 8.3, 6.9 Hz, 7H), 4.33 (dd, J = 7.9, 4.6 Hz, 1H), 4.27 (dd, J = 7.2, 0.8 Hz, 2H), 3.32 (dd, J = 13.8, 4.6 Hz, 1H), 3.19 (dd, J = 13.7, 8.0 Hz, 1H), 1.29 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 172.4, 167.6, 134.0, 132.1, 132.0, 127.7, 126.9, 126.8, 126.7, 125.7, 125.5, 125.4, 37.1, 14.1. HRMS (ESI) m/z $[M+H]^+$ calcd for $\text{C}_{28}\text{H}_{26}\text{NO}_2$ 408.1884, found 408.1885



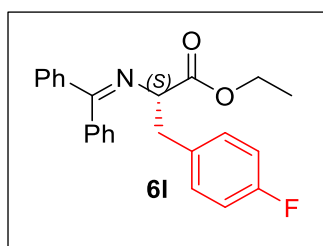
Ethyl 3-(3,5-bis(trifluoromethyl)phenyl)-2-((diphenylmethylene)amino)propanoate (6i): Yellow oil, 43.42 mg, 88% yield. Silica gel (petroleum ether–ethyl acetate: 98:2 to 90:10) afforded the pure alkylated product. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/2-propanol = 0.44/0.06, flow rate = 0.8 mL/min, wavelength = 210 nm, retention time; 18.0 min (major) and 20.5 min (minor): $[\alpha]_{\text{D}}^{28} = -120.60$ (c = 1.0, CHCl_3 ; 53% ee); ^1H NMR (500 MHz, Chloroform-d) δ 7.70 (m, 1H), 7.66 – 7.58 (d, J = 13.3 Hz, 1H), 7.54 – 7.50 (d, J = 8.3 Hz, 4H), 7.49 (t, J = 7.7 Hz, 1H), 7.39 (dd, J = 8.6, 5.7 Hz, 2H), 7.32 (q, J = 7.4 Hz, 4H), 4.29 – 4.22 (m, 2H), 4.20 (d, J = 7.1 Hz, 1H), 3.37 (d, J = 4.7 Hz, 2H), 1.65 (t, J = 7.8 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 171.9, 170.9, 142.0, 140.6, 139.9, 139.2, 132.4, 131.1, 130.6, 129.0, 128.9, 128.8, 128.7, 128.7, 122.2, 122.2, 121.2, 120.9, 120.3, 115.9, 66.1, 61.6, 61.4, 31.9, 14.1. HRMS (ESI) m/z $[M]^+$ calcd for $\text{C}_{26}\text{H}_{21}\text{F}_6\text{NO}_2$ 493.1476, found 493.1477



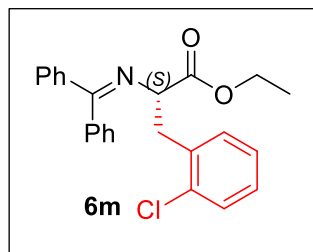
Ethyl 2-((diphenylmethylene)amino)-3-(3-fluorophenyl)propanoate (6j): Light yellow oil, 33.70 mg, 90% yield. Silica gel (petroleum ether–ethyl acetate: 98:2 to 90:10) afforded the pure alkylated product. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol = 0.45/0.05, flow rate = 0.8 mL/min, wavelength = 210 nm, retention time; 16.6 min (major) and 18.8 min (minor): $[\alpha]^{28}_D = -181.30$ ($c = 1.0$, CHCl_3 ; 86.4% ee); ^1H NMR (500 MHz, CHCl_3) δ 7.54 (d, $J = 7.4$ Hz, 1H), 7.42 – 7.36 (m, 1H), 7.13 – 7.10 (m, 4H), 7.09 (d, $J = 1.3$ Hz, 1H), 7.05 – 7.02 (m, 2H), 7.00 (d, $J = 3.6$ Hz, 1H), 6.98 (d, $J = 8.3$ Hz, 1H), 6.93 – 6.88 (m, 1H), 6.71 – 6.67 (m, 1H), 4.13 – 4.10 (m, 3H), 3.45 (dd, $J = 14.3, 5.2$ Hz, 1H), 3.34 (dd, $J = 14.4, 10.2$ Hz, 1H), 1.19 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (126 MHz, CHCl_3 -d) δ 171.7, 170.8, 163.9, 161.9, 141.6, 141.5, 139.2, 135.2, 132.4, 130.0, 129.7, 129.6, 128.4, 128.3, 128.2, 125.0, 124.1, 124.1, 116.4, 116.2, 116.2, 116.0, 114.0, 114.0, 81.9, 67.8, 39.4, 14.1. HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{23}\text{FNO}_2$ 376.1613, found 376.1614



Ethyl 2-((diphenylmethylene)amino)-3-(2-fluorophenyl)propanoate (6k): Light yellow oil, 30.01 mg, 80% yield. Silica gel (petroleum ether–ethyl acetate: 98:2 to 90:10) afforded the pure alkylated product. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak OD-H, hexane/2-propanol = 0.45/0.05, flow rate = 0.5 mL/min, wavelength = 210 nm, retention time; 16.4 min (major) and 19.0 min (major): $[\alpha]^{28}_D = -180.7$ ($c = 1.0$, CHCl_3 ; 71.5% ee); ^1H NMR 500 MHz, CDCl_3) δ 7.41 – 7.38 (m, 5H), 7.33 – 7.28 (m, 3H), 7.16 – 7.08 (m, 4H), 7.09 – 7.05 (m, 2H), 4.22 (m, 2H), 4.16 (m, 1H), 3.22 (m, 1H), 3.14 (dd, $J = 13.4, 9.4$ Hz, 1H), 1.08 (m, 3H). ^{13}C NMR (126 MHz, CHCl_3 -d) δ 171.7, 170.8, 161.7, 159.4, 130.2, 130.1, 129.5, 129.4, 124.1, 124.0, 123.4, 123.4, 114.8, 114.6, 67.8, 39.4, 14.1. HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{23}\text{FNO}_2$ 376.1713, found 376.1712.



Ethyl 2-((diphenylmethylene)amino)-3-(4-fluorophenyl)propanoate (6l): Light yellow oil, 33.65 mg, 90% yield. Silica gel (petroleum ether–ethyl acetate: 98:2 to 90:10) afforded the pure alkylated product. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak OD-H, hexane/2-propanol = 0.45/0.05, flow rate = 0.5 mL/min, wavelength = 210 nm, retention time; 34.4 min (major) and 40.9 min (minor): $[\alpha]^{28}_D = -175.70$ ($c = 1.0$, CHCl_3 ; 99.6% ee); ^1H NMR (500 MHz, CHCl_3 -d) δ 7.29 (d, $J = 3.5$ Hz, 1H), 7.28 (d, $J = 1.9$ Hz, 3H), 7.28 (s, 2H), 7.04 (d, $J = 9.3$ Hz, 1H), 6.92 (t, $J = 8.7$ Hz, 1H), 6.71– 6.68 (m, 6H), 3.82 (dd, $J = 9.4, 7.1$ Hz, 3H), 3.58 (dd, $J = 9.3, 7.1$ Hz, 2H), 1.02 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (126 MHz, CHCl_3 -d) δ 171.7, 170.8, 161.9, 160.4, 139.2, 135.2, 132.4, 130.0, 129.7, 129.6, 128.4, 128.3, 128.2, 127.5, 127.4, 125.0, 124.1, 124.0, 123.4, 115.4, 115.3, 114.0, 81.9, 67.8, 39.4, 14.1. HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{23}\text{FNO}_2$ 376.1713, found 376.1714



Ethyl 3-(2-chlorophenyl)-2-((diphenylmethylene)amino)propanoate (6m): Colorless oil, 36.86 mg, 94% yield. Silica gel (petroleum ether–ethyl acetate: 98:2 to 90:10) afforded the pure alkylated product. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak OD-H, hexane/2-propanol = 0.48/0.02, flow rate = 1.0 mL/min, 40 °C wavelength = 210 nm, retention time; 31.6 min (major) and 40.7 min (minor): $[\alpha]^{28}_{\text{D}} = -179.60$ ($c = 1.0$, CHCl_3 ; 83.2% ee); ^1H NMR (500 MHz, Chloroform- d) δ 7.35 – 7.32 (m, 3H), 7.31-7.28 (dd, $J = 6.1, 3.0$ Hz, 4H), 7.20-7.17 (d, $J = 4.9$ Hz, 6H), 4.07 (tq, $J = 7.1, 3.2$ Hz, 3H), 3.88 (d, $J = 7.0$ Hz, 1H), 3.69 – 3.66 (m, 1H), 1.08 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (126 MHz, Chloroform- d) δ 171.9, 170.6, 139.3, 137.6, 136.3, 135.8, 134.5, 132.4, 130.0, 129.3, 128.2, 128.0, 127.7, 126.5, 126.4, 61.6, 60.5, 31.9, 14.1. HRMS (ESI) m/z $[\text{M}]^+$ calcd for $\text{C}_{24}\text{H}_{22}\text{ClNO}_2$ 391.1339, found 391.1338.