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A highly α-regioselective $In(OTf)_3$-catalyzed *N*-nucleophilic substitution of cyclic Baylis–Hillman adducts with aromatic amines

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ABSTRACT

The highly α-regioselective *N*-nucleophilic substitution of B–H adducts bearing five (**1a**–**f**) or six-membered ring (**5a**–**e**) moieties with aromatic amines (**2a**–**e**) was developed under the catalysis of $In(OTf)_3$ (10 mol%). During the reaction the allylic rearrangement from γ-product to α-product occurred, resulting in thermodynamically stable α-product predominately.

1. Introduction

Baylis–Hillman (B–H) adducts, which possess allylic hydroxyl and Michael acceptor units, have been illustrated as valuable synthons and starting materials for the synthesis of various biologically active molecules.[1] Recently B–H adduct as an electrophilic substrate has achieved fruitful results in the allylic substitution reactions with various nucleophiles, including *C*-nucleophiles such as arenes, hetero-arenes,[2] and carbonion,[3] as well as hetero-nucleophiles such as the compounds bearing –OH,[4] –SH,[5] and –NH[6] groups. Among them, the carbon–nitrogen bond formation by *N*-nucleophilic substitution plays an important role for the diversity of synthetic compounds with biological activities.[1,6,11a]

Regioselective introductions of nucleophiles at either the α- or γ-position of the B–H adduct have become powerful tools in synthetic organic chemistry.[7] Allylic substitution of most acyclic B–H adducts could achieve regiocontrol either at γ-position by Lewis acid catalysis and inorganic base promotion,[8] or at α-position mainly by organic base catalysts.[9] On the other hand, condensation of polycyclic ring system is the effort for the synthesis of heterocyclic compounds and natural products. Cyclic B–H adducts derived from cyclic enones[10] could acquire great success in generating fused cyclic framework.[11] However, the allylic alkylation of cyclic B–H adducts could be different from most acyclic B–H adducts due to its unsymmetrically substituted allyl structure. The development of an efficient catalyst for the highly regioselective allylic substitution of cyclic B–H adducts with *N*-nucleophiles is still a challenging problem.

Meanwhile, the B–H acetate was employed in the nucleophilic substitutions better than the B–H adduct bearing allylic alcohol unit, because hydroxyl group was usually considered as an inefficient leaving group. However, the advantages of directly using allyl alcohol as an allylic reagent were noteworthy: no further functionalization was required for the activation of hydroxyl group and water was the sole by-product after the reaction. Although many methods could be used to proceed the allylic amination of B–H acetates, the *N*-nucleophilic substitution of B–H alcohols was seldom reported. Instead of allylic amination, the reaction of most B–H alcohols with amines afforded related Michael addition products.[12]

Recently, we reported a highly α-regioselective Lewis acid (AgOTf)-catalyzed allylation of cyclic B–H acetates with indoles as *C*-nucleophiles.[13] As a continuation of our research in the allylations with cyclic B–H adducts as the allylic reagents, herein, we want to report highly α-regioselective *N*-nucleophilic substitution of cyclic B–H adducts bearing allylic alcohol unit with aromatic amines catalyzed by $In(OTf)_3$.

2. Results and discussion

2.1. Catalytic allylic substitution of cyclic B–H adduct 1a with aniline 2a

Initially, the reaction of cyclic B–H adduct **1a** and a simple aromatic amine, aniline **2a** was carried out under various conditions

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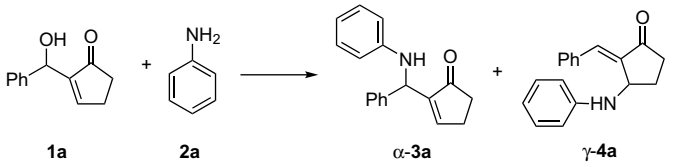
Table 1
Catalytic reactions of **1a** with **2a**[a]



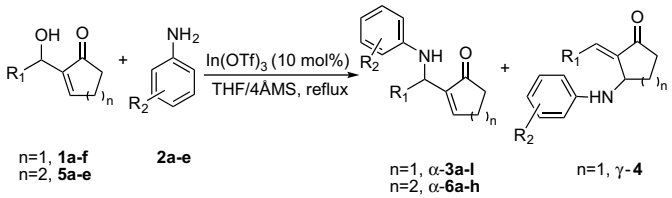
1a **2a** α-**3a** γ-**4a**

Entry	Catalyst	Solvent	Time (h)	Yield[b] of α-**3a** (%)	α/γ[c]
1	AgOTf	DCM	12	—[d]	
2	$InBr_3$	DCM	12	3	—[e]
3	$Zn(OTf)_2$	DCM	10	10	—[e]
4	$Sc(OTf)_3$	DCM	10	18	—[e]
5	I_2	THF	12	—[d]	
6	$In(OTf)_3$	DCM	12	28	16:1
7	$In(OTf)_3$	THF	12	37	15:1
8	$In(OTf)_3$	THF/4 Å MS	12	63	12:1
9	DABCO	THF	32	—[d]	
10[f]	$Pd(PPh)_4$	THF	24	62	1.9:1
11[f]	—	THF/4 Å MS	24	—[d]	

[a] Reaction in refluxing solvent; catalyst loading: 10 mol %.
[b] Yield of isolated product.
[c] Determined by ^1H NMR of crude reaction mixture.
[d] No product determined.
[e] No γ-product detected.
[f] Reaction temperature: room temperature.

(Table 1). Unfortunately, AgOTf did not exhibit any catalytic activity (entry 1). Similarly, in the cases of $InBr_3$, $Zn(OTf)_2$, $Sc(OTf)_3$, and molecule I_2 the reaction did not take place or proceeded sluggishly (entries 2–5). The results indicated that the aromatic amines were less reactive *N*-nucleophiles for the substitution reaction with cyclic B–H adduct. Interestingly, $In(OTf)_3$ was found to be more effective as a catalyst (10 mol %) (entries 6 and 7).

To our delight, when molecular sieve (4 Å MS) was added as an additive into the reaction mixture, which may played a role for absorbing the water produced during the reaction, the reaction proceeded smoothly to give the allylation products, a mixture of α-**3a** and γ-**4a**, with the high α-regioselectivity (α-/γ-product=12:1) in 63% isolated yield of α-**3a** in THF (entry 8).



n=1, **1a-f**
n=2, **5a-e**
2a-e
n=1, α-**3a-l**
n=2, α-**6a-h**
n=1, γ-**4**

Scheme 1.

Although DABCO and palladium catalyst exhibited good catalytic ability for the reaction of acyclic B–H adducts with *N*-nucleophiles,[6] DABCO lost its catalytic ability in the reaction of cyclic B–H adduct **1a** (entry 10). Pd-catalyzed reaction of **1a** with **2a** provided poor regioselectivity (α-/γ-product=1.9:1, entry 11). In the absence of catalyst, the reaction did not occur at all even though 4 Å MS was added, and the starting materials were recovered (entry 11).

2.2. The $In(OTf)_3$-catalyzed allylic substitution of cyclic B–H adducts with aromatic amines

Subsequently, the reactions of various cyclic B–H adducts bearing five (**1a**–**f**) or six-membered ring (**5a**–**e**) units and aromatic amines (**2a**–**e**) were carried out in the presence of $In(OTf)_3$ (10 mol %) in refluxing THF with 4 Å MS to give allylic substitution products in good isolated yields with high α-regioselectivities (Scheme 1, Table 2). For B–H adducts with five-membered ring, in some cases a few γ-products could be isolated, while for B–H adducts with six-membered ring, the reaction became slow, but no γ-products were observed in the product mixture. It was found that when R_1 was cyclohexyl group (**1f**), the reaction with aniline **2a** catalyzed by $In(OTf)_3$ could also give the good yield (Table 2, entry 9).

Table 2
$In(OTf)_3$-catalyzed allylation reactions of B–H adducts with aromatic amines

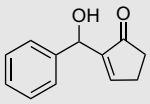
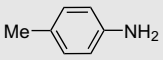
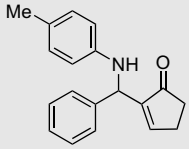
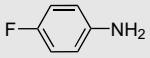
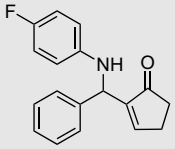
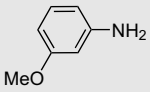
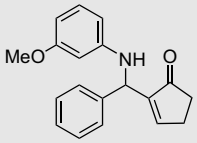
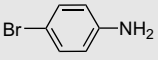
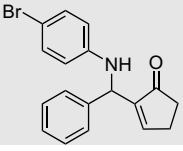
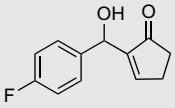
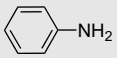
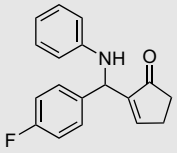
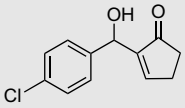
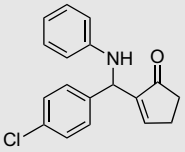
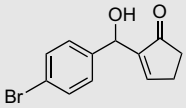
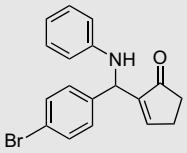
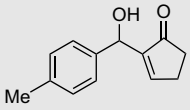
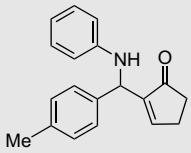
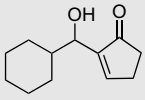
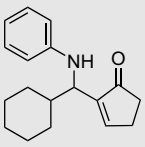
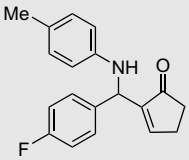
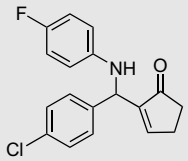
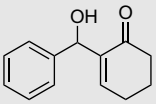
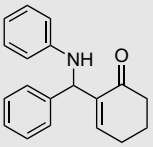
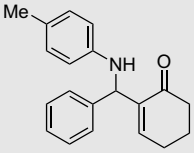
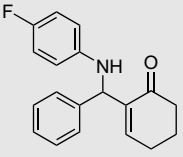
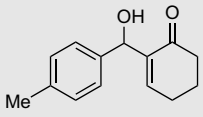
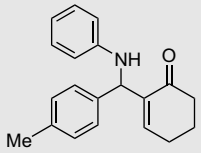
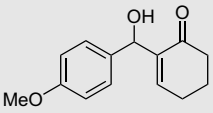
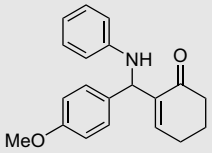
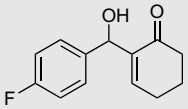
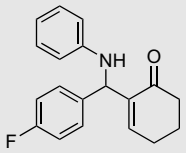
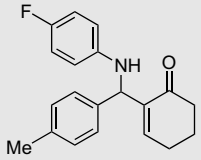
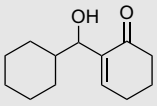
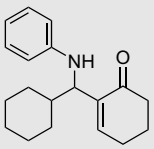
Entry	B–H adduct		Amine		Time (h)	α-Product		Yield[a] (%)	α/γ[b]
1	**1a**		**2b**		12	α-**3b**		65	10:1
2	**1a**		**2c**		12	α-**3c**		64	11:1
3	**1a**		**2d**		12	α-**3d**		67	13:1
4	**1a**		**2e**		24	α-**3e**		62	8:1

Table 2 (*continued*)

Entry	B–H adduct		Amine	Time (h)	α-Product	Yield[a] (%)	α/γ[b]
5	**1b**		**2a**		α-**3f**		67	9:1
6	**1c**		**2a**		12	α-**3g**		66	15:1
7	**1d**		**2a**		12	α-**3h**		63	15:1
8	**1e**		**2a**		12	α-**3i**		62	10:1
9	**1f**		**2a**		12	α-**3j**		75	[c]
10	**1b**		**2b**		12	α-**3k**		70	13:1
11	**1c**		**2c**		12	α-**3l**		65	14:1
12	**5a**		**2a**		22	α-**6a**		75	[c]
13	**5a**		**2b**		20	α-**6b**		68	[c]
14	**5a**		**2c**		20	α-**6c**		71	[c]

(*continued on next page*)

Table 2 (*continued*)

Entry	B–H adduct	Amine	Time (h)	α-Product	Yield[a] (%)	α/γ[b]
15	**5b** 	**2a**	22	α-**6d** 	65	[c]
16	**5c** 	**2a**	45	α-**6e** 	67	[c]
17	**5d** 	**2a**	22	α-**6f** 	65	[c]
18	**5b**	**2c**	22	α-**6g** 	80	[c]
19	**5e** 	**2a**	72	α-**6h** 	79	[c]

[a] Isolated yield.
[b] Determined by ^{1}H NMR of crude reaction mixture.
[c] No γ-product detected in the product mixture.

2.3. Allylic rearrangement from γ- to α-product

In order to explicate the origin of the high α-regioselectivity, the relationship between the conversion in the reaction of **1a** with **2a** catalyzed by $In(OTf)_3$/4 Å MS refluxed in THF and the ratio of α-**3a**/γ-**4a** in the product mixture was examined based on ^{1}H NMR data with reaction time. As shown in Table 3, initially the ratios of α- and γ-product were moderate (4.3:1–6.5:1). With increasing time, the conversion reached 100%, while the ratio of α- to γ-product became higher up to 12:1.

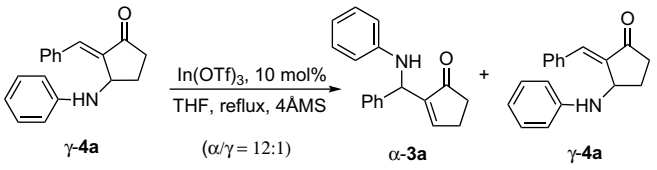
Moreover, under the reaction conditions, the pure γ-**4a** was treated in the presence of the catalyst $In(OTf)_3$ (10 mol %) for 12 h, the product mixture was found to compose of α-**3a** and γ-**4a** with the ratio as high as 12:1 (Scheme 2). However, under the same conditions, the treatment of pure α-**3a** could not observe the isomerization of α-**3a** to γ-**4a**. It was suggested that there should be an allylic rearrangement reaction[14] from γ-product to α-product occurred in the course of the reaction of cyclic B–H adduct with aromatic *N*-nucleophiles, eventually reaching at thermodynamical equilibrium between α- and γ-product with α-regioselectivity as high as 12:1.

In summary of the experimental results, a plausible mechanism could be proposed in Scheme 3. In $In(OTf)_3$-catalyzed reaction, through chelated coordination mode **A**, instead of mono-coordination mode **B**, which may result in Michael addition, the hydroxyl group would be activated and the nucleophiles could attack at both α- and γ-position. However, with the reaction proceeding, the allylic rearrangement from γ-product to α-product occurred. It

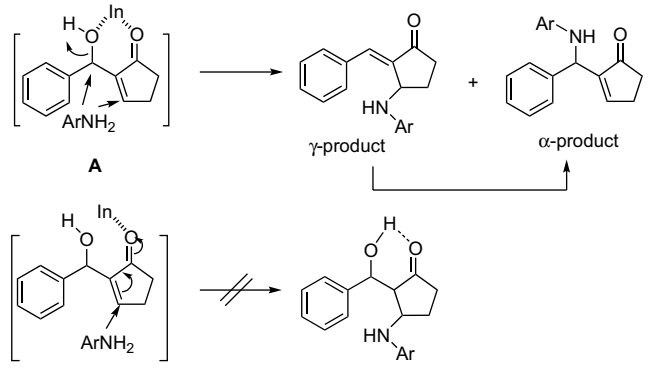
Table 3
Relationship between conversion and ratio of α-3a to γ-4a with reaction time[a]

Time	10 min	30 min	1 h	2 h	12 h	20 h
Conver. (%)	73	75	86	87	100	100
α-**3a**/γ-**4a**	4.3:1	6.5:1	9.0:1	9.2:1	11:1	12:1

[a] Determined by ^{1}H NMR.



Scheme 2.



Scheme 3.

can be found that α-product is more thermodynamically stable compound, resulting in α-selection predominately.

3. Conclusion

Highly α-regioselective $In(OTf)_3$-catalyzed *N*-nucleophilic substitution of cyclic B–H adducts with aromatic amines was developed. During the course of the reaction, allylic rearrangement from γ-product to α-product occurred, utilizing this rearrangement reaction, α-regiocontrol to the *N*-nucleophilic substitution of cyclic B–H adducts could be realized. The synthetic method provided an efficient route to aromatic allylic amine bearing cyclic unsaturated ketone unit.

4. Experimental

4.1. General

IR spectra were recorded with a Perkin–Elmer 782 IR spectrometer. ^1H NMR and ^{13}C NMR spectra were obtained in $CDCl_3$ at room temperature with a Bruker DMX-300 (300 MHz) spectrometer. Chemical shifts are given in parts per million relative to tetramethylsilane (TMS). Mass spectra were recorded with a Bruker APEX-2 spectrometer. Elemental analyses were performed with a Carlo Erba 1102 Element Analysis instrument. Melting points were measured with a Beijing-Taike X-4 apparatus and are uncorrected. Unless otherwise noted, all reagents were obtained from commercial suppliers and were used without further purification. According to reference's method,[10] the cyclic B–H adducts (**1a–f** and **5a–e**) were synthesized.

4.2. Typical procedure for allylation substitution reactions of cyclic B–H adducts with aromatic amines

To a suspension of 2-[hydroxy(phenyl)methyl]cyclopent-2-enone **1a** (56.4 mg, 0.3 mmol), $In(OTf)_3$ (16.9 mg, 0.03 mmol), and 4 Å MS (200 mg) in THF (2 mL), aniline **2a** (41 μL, 0.45 mmol) was added, followed by stirring in refluxing THF under a nitrogen atmosphere for 12 h. After the reaction finished, the reaction mixture was cooled down and filtered through a pad of diatomite. The filtrate was washed with saturated $NaHCO_3$ and extracted with $CHCl_3$. The combined organic phase was dried over Na_2SO_4 and evaporated under vacuum to give crude product, which was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate=4:1) to give yellow powder α-**3a** (51.4 mg, 65% yield) and yellow foam γ-**4a** (6.5 mg, 8% yield). The α/γ value was determined by the ^1H NMR absorptions of the product mixture at 5.31 and 4.92 ppm.

*4.2.1. 2-[(Phenylamino)(phenyl)methyl]cyclopent-2-enone (α-**3a**)*

Yellow solid, mp: 142–143 °C. FTIR (KBr): ν 3395, 3052, 2919, 1692, 1599, 1501, 749, 694 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.44 (m, 2H), 2.58 (m, 2H), 4.51 (br, 1H), 5.31 (s, 1H), 6.55 (d, *J*=8.6 Hz, 2H), 6.69 (t, 1H, *J*=7.3 Hz), 7.12 (dd, *J*=8.5, 7.4 Hz, 2H), 7.24–7.48 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.5, 35.3, 55.0, 113.7, 118.0, 127.0, 127.6, 128.7, 129.1, 141.0, 146.8, 147.0, 159.5, 208.0. HRMS (EI): *m*/*z* calcd for $C_{18}H_{17}NO$ (M^+): 263.1310, found: 263.1308.

*4.2.2. (E)-2-Benzylidene-3-(phenylamino)cyclopentanone (γ-**4a**)*

A yellow foam. FTIR (KBr): ν 3368, 3053, 2923, 1709, 1609, 1501, 1444, 1310, 1183, 1079, 751, 695, 514 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.98–2.09 (m, 1H), 2.34–2.46 (m, 2H), 2.52–2.62 (m, 1H), 3.97 (br, 1H), 4.92 (br, 1H), 6.68 (d, *J*=8.3 Hz, 2H), 6.81 (t, *J*=7.3 Hz, 1H), 7.24–7.37 (m, 5H), 7.57–7.61 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.5, 34.1, 52.1, 112.5, 117.1, 128.1, 128.5, 129.4, 130.4, 132.9, 135.8, 136.2, 145.1, 205.7. HRMS (EI): *m*/*z* calcd for $C_{18}H_{17}NO$ (M^+): 263.1310, found: 263.1308.

*4.2.3. 2-[(p-Toluidino)(phenyl)methyl]cyclopent-2-enone (α-**3b**)*

Yellow solid, mp: 141–142 °C. FTIR (KBr): ν 3421, 2986, 1745, 1563, 1490, 1372, 1308, 1098, 743 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.19 (s, 3H), 2.41 (m, 2H), 2.55 (m, 2H), 4.39 (br, 1H), 5.27 (br, 1H), 6.47 (d, *J*=8.3 Hz, 2H), 6.92 (d, *J*=8.3 Hz, 2H), 7.20–7.46 (m, 6H). The α/γ value was determined by the ^1H NMR absorptions of the product mixture at 5.27 and 4.91 ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.3, 26.6, 35.4, 55.2, 113.9, 127.1, 127.1, 127.5, 128.7, 128.6, 141.2, 144.7, 146.9, 159.6, 208.2. HRMS (EI): *m*/*z* calcd for $C_{19}H_{19}NO$ (M^+): 277.1467, found: 277.1465.

*4.2.4. 2-[(4-Fluorophenylamino)(phenyl)methyl]cyclopent-2-enone (α-**3c**)*

White solid, mp: 125–127 °C. FTIR (KBr): ν 3376, 3058, 2922, 1695, 1621, 1511, 1217, 823, 780, 705, 516 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.09 (br s, 1H), 7.56 (d, *J*=7.7 Hz, 1H), 7.38 (d, *J*=8.9 Hz, 1H), 7.19–7.14 (m, 2H), 7.08–7.03 (m, 1H), 6.88–6.83 (m, 1H), 6.77 (d, *J*=1.6 Hz, 1H), 6.70 (d, *J*=8.0 Hz, 1H), 5.89, 5.86 (dd, *J*=1.0, 9.3 Hz, 2H), 5.81 (d, *J*=11.3 Hz, 1H), 5.29 (d, *J*=11.3 Hz, 1H), 4.13–4.03 (m, 2H), 1.02 (t, *J*=7.1 Hz, 3H). The α/γ value was determined by the ^1H NMR absorptions of the product mixture at 5.28 and 4.87 ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.6, 35.3, 55.6, 114.7 (*J*=7.35 Hz), 115.6 (*J*=22.2 Hz), 127.0, 127.6, 128.8, 140.9, 143.3, 146.6, 156.1 (*J*=−234.2 Hz), 159.9, 208.2. HRMS (EI): *m*/*z* calcd for $C_{18}H_{16}NOF$ (M^+): 281.1216, found: 281.1214.

*4.2.5. 2-[(3-Methoxyphenylamino)(phenyl)methyl]cyclopent-2-enone (α-**3d**)*

Yellow solid, mp: 123–125 °C. FTIR (film): ν 3409, 2923, 1747, 1562, 1459, 1303, 1183, 1016, 740 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.40–2.43 (m, 2H), 2.54–2.57 (m, 2H), 3.68 (s, 3H), 4.56 (br, 1H), 5.30 (s, 1H), 6.10 (s, 1H), 6.17 (dd, *J*=8.0, 1.0 Hz, 1H), 6.25 (dd, *J*=6.8, 1.3 Hz, 1H), 7.01 (t, *J*=8.1 Hz, 1H), 7.21–7.39 (m, 5H), 7.46 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.6, 35.4, 55.0, 55.0, 99.8, 103.2, 106.7, 127.0, 127.6, 128.8, 129.9, 141.0, 146.6, 148.4, 159.8, 160.7, 208.2. HRMS (EI): *m*/*z* calcd for $C_{19}H_{19}NO_2$ (M^+): 293.1416, found: 293.1414.

*4.2.6. 2-[(4-Bromophenylamino)(phenyl)methyl]cyclopent-2-enone (α-**3e**)*

Yellow solid, mp: 152–153 °C. FTIR (KBr): ν 3377, 3054, 2918, 2853.2, 1690, 1592, 1495, 1290, 1242, 814, 700, 501 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.43 (m, 2H), 2.57 (m, 2H), 4.65 (br s, 1H), 5.26 (s, 1H), 6.42 (d, *J*=7.8 Hz, 2H), 7.16–7.37 (m, 7H), 7.44 (s, 1H). The α/γ value was determined by the ^1H NMR absorptions of the product mixture at 5.30 and 4.91 ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.6, 35.3, 55.0, 109.6, 115.3, 127.0, 127.7, 128.8, 131.8, 140.5, 145.9, 146.3, 160.0, 208.2. HRMS (FAB): *m*/*z* calcd for $C_{18}H_{16}NOBr$ (M^+): 341.0415 and 343.0395, found: 341.0418 and 343.0398.

*4.2.7. 2-[(Phenylamino)(4-fluorophenyl)methyl]cyclopent-2-enone (α-**3f**)*

Yellow solid, mp: 104–105 °C. FTIR (KBr): ν 3380, 3053, 2922, 1695, 1601, 1504, 1434, 1225, 1004, 839, 748, 695, 518 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.42 (m, 2H), 2.56 (m, 2H), 4.50 (br s, 1H), 5.28 (s, 1H), 6.53 (d, *J*=8.2 Hz, 2H), 6.69 (t, *J*=7.3 Hz, 1H), 6.98 (t, *J*=8.6 Hz, 2H), 7.10 (m, 2H), 7.33–7.37 (m, 2H), 7.45 (s, 1H). The α/γ value was determined by the ^1H NMR absorptions of the product mixture at 5.28 and 4.87 ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.6, 35.4, 54.3, 113.8, 115.6 (*J*=21.3 Hz), 118.1, 128.7 (*J*=8.0 Hz), 129.2, 136.8, 146.6, 146.8, 159.8, 162.2 (*J*=−244 Hz). HRMS (EI): *m*/*z* calcd for $C_{18}H_{16}NOF$ (M^+): 281.1216, found: 281.1214.

*4.2.8. 2-[(Phenylamino)(4-chlorophenyl)methyl]cyclopent-2-enone (α-**3g**)*

Yellow powder, mp: 138–140 °C. FTIR (KBr): ν 3381, 3053, 2921, 1695, 1600, 1498, 1316, 1258, 1092, 1007, 747, 696, 512 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.41–2.44 (m, 2H), 2.57–2.59 (m, 2H), 4.52 (br s, 1H), 5.28 (s, 1H), 6.52–6.54 (m, 2H), 6.70 (t, *J*=7.3 Hz, 1H),

7.08–7.14 (m, 2H), 7.23–7.28 (m, 4H), 7.45 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.6, 35.3, 54.4, 113.8, 118.2, 128.4, 128.9, 129.2, 133.3, 139.6, 146.4, 146.7, 159.9, 208.0. HRMS (EI): *m*/*z* calcd for $C_{18}H_{16}NOCl$ (M^+): 297.0920, found: 297.0918.

*4.2.9. 2-[(Phenylamino)(4-bromophenyl)methyl]cyclopent-2-enone (α-**3h**)*

Yellow solid, mp: 151–152 °C. FTIR (KBr): ν 3347, 3051.8, 2915, 2853, 1693, 1599, 1495, 1433, 1258, 1003, 826, 747, 695, 512 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.39–2.47 (m, 2H), 2.60 (m, 2H), 4.55 (br s, 1H), 5.29 (s, 1H), 6.54 (s, 1H), 6.57 (s, 1H), 6.72 (t, *J*=7.3 Hz, 1H), 7.11–7.16 (m, 2H), 7.28–7.31 (m, 2H), 7.44–7.48 (m, 3H). The α/γ value was determined by the ^{1}H NMR absorptions of the product mixture at 5.29 and 4.89 ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.6, 35.3, 54.4, 113.8, 118.2, 121.4, 128.8, 129.2, 131.9, 140.2, 146.3, 146.6, 156.0, 208.0. HRMS (EI): *m*/*z* calcd for $C_{18}H_{16}NOBr$ (M^+): 341.0415 and 343.0395, found: 341.0413 and 343.0392.

*4.2.10. 2-[(Phenylamino)(p-tolyl)methyl]cyclopent-2-enone (α-**3i**)*

Yellow solid, mp: 128–129 °C. FTIR (KBr): ν 3382, 3049, 3021, 2921, 2858, 1695, 1600, 1505, 1434, 1315, 1259, 1185, 746, 694, 516 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H), 2.44–2.48 (m, 2H), 260 (m, 2H), 4.54 (br s, 1H), 5.32 (s, 1H), 6.57 (s, 1H), 6.60 (s, 1H), 6.72 (t, *J*=7.3 Hz, 1H), 7.12–7.18 (m, 4H), 7.31 (s, 1H), 7.33 (s, 1H), 7.51 (m, 1H). The α/γ value was determined by the ^{1}H NMR absorptions of the product mixture at 5.32 and 4.91 ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1, 26.6, 35.4, 54.7, 113.7, 117.9, 127.0, 129.2, 129.5, 137.3, 138.0, 146.8, 147.0, 159.6, 208.3. HRMS (EI): *m*/*z* calcd for $C_{19}H_{19}NO$ (M^+): 277.1467, found: 277.1469.

*4.2.11. 2-[(Phenylamino)(cyclohexyl)methyl]cyclopent-2-enone (α-**3j**)*

Yellow solid, mp: 78–79 °C. FTIR (KBr): ν 3382, 3053, 2921, 2850, 2361, 1690, 1597, 1502, 1441, 1251, 746, 686 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90–1.28 (m, 5H), 1.57–1.80 (m, 5H), 1.92 (d, *J*=12.8 Hz, 1H), 2.40–2.42 (m, 2H), 2.52–2.55 (m, 2H), 4.01 (d, *J*=6.8 Hz, 1H), 4.22 (s, 1H), 6.50 (d, *J*=8.6 Hz, 2H), 6.63 (t, *J*=7.3 Hz, 1H), 7.10 (m, 2H), 7.33 (t, *J*=2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.2, 26.4. 29.4, 30.3, 35.4, 41.3, 55.7, 113.2, 117.1, 129.2, 145.7, 147.6, 159.5, 209.3. HRMS (EI): *m*/*z* calcd for $C_{18}H_{23}NO$ (M^+): 269.1780, found: 269.1783.

*4.2.12. 2-[(p-Toluidino)(4-fluorophenyl)methyl]cyclopent-2-enone (α-**3k**)*

Yellow solid, mp: 111–112 °C. FTIR (KBr): ν 3385, 3031, 2924, 1668, 1511, 1377, 1312, 1217, 1165, 821, 774, 703, 515 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.20 (s, 3H), 2.40–2.44 (m, 2H), 2.55–2.58 (m, 2H), 4.37 (br s, 1H), 5.26 (s, 1H), 6.45 (d, *J*=8.4 Hz, 2H), 6.91–7.01 (m, 4H), 7.33–7.37 (m, 2H), 7.45 (t, *J*=2.6 Hz, 1H). The α/γ value was determined by the ^{1}H NMR absorptions of the product mixture at 5.26 and 4.85 ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.4, 26.6, 35.4, 54.6, 113.9, 115.5 (d, *J*=21.4 Hz), 127.4, 128.7 (d, *J*=8.0 Hz), 129.7, 137.0, 144.5, 146.8, 159.7, 162.2 (d, *J*=244.2 Hz). HRMS (EI): *m*/*z* calcd for $C_{19}H_{18}NOF$ (M^+): 295.1372, found: 295.1375.

*4.2.13. 2-[(4-Fluorophenylamino)(4-chlorophenyl)methyl]-cyclopent-2-enone (α-**3l**)*

Yellow solid, mp: 107–111 °C. FTIR (KBr): ν 3378, 3048, 2922, 2862, 1696, 1618, 1512, 1220, 1093, 1008, 818, 514 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.43 (m, 2H), 2.58 (m, 2H), 4.47 (br s, 1H), 5.21 (s, 1H), 6.44–6.49 (m, 2H), 6.81 (t, *J*=8.7 Hz, 2H), 7.26–7.34 (m, 4H), 7.43 (t, *J*=2.6 Hz, 1H). The α/γ value was determined by the ^{1}H NMR absorptions of the product mixture at 5.21 and 4.82 ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.6, 35.2, 55.1, 114.8 (*J*=7.4 Hz), 115.6 (*J*=−22.3 Hz), 128.3, 128.9, 133.4, 139.5, 143.0, 146.3, 156.2 (d, *J*=234.8 Hz), 159.9, 207.9. HRMS (EI): *m*/*z* calcd for $C_{18}H_{15}NOFCl$ (M^+): 315.0826, found: 315.0829.

*4.2.14. 2-[(Phenylamino)(phenyl)methyl]cyclohex-2-enone (α-**6a**)*

Yellow powder, mp: 124–125 °C. FTIR (KBr): ν 3392, 3052, 3031, 2928, 2875, 1667, 1600, 1500, 1426, 1376, 1315, 1251, 1172, 748, 697, 512 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.95 (m, 2H), 2.39 (m, 4H), 4.21 (br s, 1H), 5.42 (s, 1H), 6.50–5.53 (m, 2H), 6.67 (t, *J*=7.3 Hz, 1H), 7.02 (t, *J*=4.1 Hz, 1H), 7.08–7.04 (m, 2H), 7.19–7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.8, 38.7, 56.7, 113.5, 117.7, 127.3, 127.4, 128.6, 129.2, 139.4, 141.8, 146.7, 147.1, 198.5. HRMS (EI): *m*/*z* calcd for $C_{19}H_{19}NO$ (M^+): 277.1467, found: 277.1469.

*4.2.15. 2-[(p-Toluidino)(phenyl)methyl]cyclohex-2-enone (α-**6b**)*

Yellow solid, mp: 139–141 °C. FTIR (KBr): ν 3388, 3048, 3021, 2923, 2862, 1667, 1598, 1503, 1427, 1374, 1313, 1249, 1171, 810, 750, 693, 510 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.91–2.04 (m, 2H), 2.20 (s, 3H), 2.36–2.46 (m, 4H), 4.08 (br s, 1H), 5.39 (s, 1H), 6.44 (d, *J*=8.3 Hz, 2H), 6.93 (d, *J*=8.3 Hz, 2H), 7.03 (t, *J*=4.0 Hz, 1H), 7.21–7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.4, 22.8, 26.0, 38.8, 47.2, 113.6, 126.9, 127.3, 128.6, 129.7, 139.6, 142.0, 144.8, 146.6, 198.6. HRMS (EI): *m*/*z* calcd for $C_{20}H_{21}NO$ (M^+): 291.1623, found: 291.1625.

*4.2.16. 2-[(4-Fluorophenylamino)(phenyl)methyl]cyclohex-2-enone(α-**6c**)*

A yellow liquid. FTIR (KBr): ν 3383, 3057, 3034, 2938, 2880, 1667, 1511, 1377, 1217, 821, 703, 515 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.90–2.03 (m, 2H), 2.37–2.49 (m, 4H), 4.16 (br s, 1H), 5.35 (s, 1H), 6.42–6.47 (m, 2H), 6.81 (d, *J*=233.6 Hz) (t, *J*=8.7 Hz, 2H), 6.99 (t, *J*=4.1 Hz, 1H), 7.27–7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.7, 26.0, 38.7, 57.6, 114.4 (*J*=7.3 Hz), 115.5 (*J*=22.2 Hz), 127.2, 127.4, 128.6, 139.4, 141.6, 143.4, 146.9, 156.0 (*J*=−233.6 Hz), 198.6. Anal. Calcd for $C_{19}H_{18}FNO$: C, 77.27; H, 6.14; N, 4.74. Found: C, 77.32; H, 6.22; N, 4.92.

*4.2.17. 2-[(Phenylamino)(p-tolyl)methyl]cyclohex-2-enone (α-**6d**)*

Yellow solid, mp: 109–111 °C. FTIR (KBr): ν 3388, 3026, 2923, 2862, 1677, 1614, 1517, 1375, 1308, 1248, 1173, 808, 702, 510 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.92–2.04 (m, 2H), 2.31 (s, 3H), 2.37–2.49 (m, 4H), 4.17 (br s, 1H), 5.39 (s, 1H), 6.51 (d, *J*=7.7 Hz, 2H), 6.68 (t, *J*=7.3 Hz, 1H), 7.04 (t, *J*=4.0 Hz, 1H), 7.09–7.15 (m, 4H), 7.22–7.25 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1, 22.8, 25.9, 38.8, 56.7, 113.4, 117.6, 127.2, 129.1, 129.3, 137.0, 138.8, 139.4, 146.4, 147.1, 198.6. HRMS (EI): calcd for $C_{20}H_{21}NO$ (M^+): 291.1623, found: 291.1626.

*4.2.18. 2-[(Phenylamino)(4-methoxyphenyl)methyl]cyclohex-2-enone (α-**6e**)*

A yellow liquid. FTIR (KBr): ν 3389, 3043, 2922, 2862, 1666, 1602, 1505, 1374, 1247, 1173, 1032, 817, 749, 694 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.92–2.04 (m, 2H), 2.35–2.44 (m, 4H), 3.76 (s, 3H), 4.16 (br s, 1H), 5.37 (s, 1H), 6.50 (d, *J*=8.2 Hz, 2H), 6.67 (t, *J*=7.3 Hz, 1H), 6.83 (d, *J*=8.7 Hz, 2H), 7.03 (t, *J*=4.1 Hz, 1H), 7.11 (t, *J*=7.7 Hz, 2H), 7.26 (d, *J*=8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.8, 25.9, 38.8, 55.3, 56.4, 113.4, 114.0, 117.6, 128.4, 129.1, 133.9, 139.4. 146.3, 147.1, 158.9, 198.6. HRMS (EI): *m*/*z* calcd for $C_{20}H_{21}NO_2$ (M^+): 307.1572, found: 307.1574.

*4.2.19. 2-[(Phenylamino)(4-fluorophenyl)methyl]cyclopent-2-enone (α-**6f**)*

White solid, mp: 104–106 °C. FTIR (KBr): ν 3394, 3061, 2929, 1664, 1604, 1503, 1425, 1375, 1314, 1224, 1163, 822, 749, 694, 519 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.68–2.04 (m, 2H), 2.36–2.44 (m, 2H), 4.18 (br s, 1H), 5.29 (s, 1H), 6.51 (d, *J*=7.7 Hz, 2H), 6.69 (t, *J*=7.3 Hz, 1H), 6.95–7.15 (m, 5H), 7.29–7.34 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.7, 25.9, 38.7, 56.5, 113.5, 115.4 (*J*=−21.4 Hz), 117.9, 128.8 (*J*=8.0 Hz), 129.2, 137.5, 139.4, 146.9, 162.1 (*J*=244.0 Hz), 198.5. HRMS (EI): *m*/*z* calcd for $C_{19}H_{18}NOF$ (M^+): 295.1372, found: 295.1375.

*4.2.20. 2-[(4-Fluorophenylamino)(p-tolyl)methyl]cyclohex-2-enone (α-**6g**)*

White solid, mp: 104–106 °C. FTIR (KBr): ν 3394, 3061, 2929, 1664, 1604, 1503, 1425, 1375, 1314, 1224, 1163, 822, 749, 694, 519 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.99–2.00 (m, 2H), 2.30 (s, 3H), 2.34–2.46 (m, 4H), 4.12 (br s, 1H, s), 5.32 (s, 1H), 6.41–6.46 (m, 2H), 6.80 (t, J=8.7 Hz, 2H), 6.98 (t, J=4.0 Hz, 1H), 7.10 (d, J=7.9 Hz, 2H), 7.22 (d, J=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1, 22.7, 25.9, 38.7, 57.3, 114.3 (J=7.3 Hz), 115.5 (J=22.2 Hz), 127.1, 129.3, 137.0, 138.6, 139.5, 143.5, 146.7, 155.9 (J=233.6 Hz), 198.6. HRMS (EI): m/z calcd for $C_{20}H_{20}NOF$ (M^+): 309.1529, found: 309.1532.

*4.2.21. 2-[(Phenylamino)(cyclohexyl)methyl]cyclohex-2-enone (α-**6h**)*

A yellow liquid. FTIR (KBr): ν 3400, 3053, 3021, 2959, 2924, 2870, 1665, 1602, 1505, 1380, 1318, 1259, 117, 1091, 1026, 802, 751, 695, 494 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.87–1.13 (m, 2H), 1.16–1.31 (m, 3H), 1.53–1.78 (m, 6H), 1.90–2.00 (m, 3H), 2.32–2.37 (m, 2H), 2.40–2.44 (m, 2H), 3.97 (d, J=7.3 Hz, 1H), 4.18 (br s, 1H), 6.48 (d, J=8.0 Hz, 2H), 6.63 (t, J=7.3 Hz, 1H), 6.78 (t, J=4.2 Hz, 1H), 7.11 (t, J=7.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.8, 24.9, 25.2, 25.3, 25.5, 28.8, 29.8, 37.9, 41.0, 58.1, 112.2, 115.8, 128.1, 137.7, 145.4, 146.8, 198.6. HRMS (EI): m/z calcd for $C_{19}H_{25}NO$ (M^+): 283.1936, found: 283.1939.

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