Formation of α-Amino Ketones: Addition of Acylzirconocene Chlorides to Imines Catalyzed by Yb(OTf)$_3$/TmsOTf and Brønsted Acids and Three-Component Reactions of Acylzirconocene Chlorides, Aldehydes, and Amines

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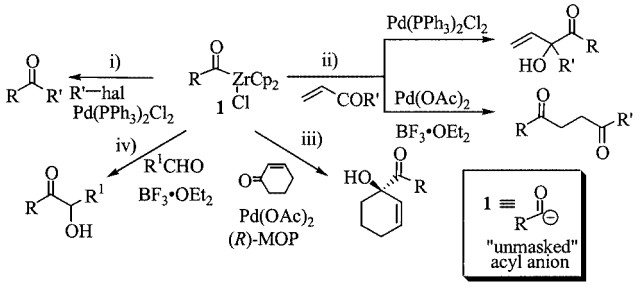
A direct preparation of α-amino ketone derivatives through treatment of acylzirconocene chlorides with *N*-benzylideneaniline derivatives, in which acylzirconocene chlorides react as "unmasked" acyl anion donors, was carried out under Yb(OTf)$_3$/TMSOTf-catalyzed conditions. The same reactions were also carried out with the use of Brønsted acids as catalyst in place of Yb(OTf)$_3$/TMSOTf. The operationally simple three-component reaction with aldehydes, anilines, and acylzirconocene chlorides affords α-amino ketone derivatives essentially in the absence of a catalyst.

Introduction

The search for new reactions of acylzirconocene chloride complexes **1**, which can be prepared by the hydrozirconation of unsaturated compounds and subsequent insertion of carbon monoxide,[1] is the focus of our current investigation. Our recent studies of the reactivity of easily accessible and stable acylzirconocene chloride derivatives **1** have opened up their potential as donors of "unmasked" acyl anions in organic synthesis. In these studies, we have reported on (i) Pd-catalyzed coupling reactions with organic halides,[2] (ii) Pd-catalyzed regiochemically adjustable nucleophilic acylation of α,β-enones,[3] (iii) Pd(OAc)$_2$[(*R*)-MOP]-catalyzed enantioselective 1,2-additions to α,β-enone derivatives,[4] and (iv) Lewis acid mediated reactions with aldehydes[5] (Scheme 1).



Scheme 1. Reactions of compounds **1** as acyl anion donors

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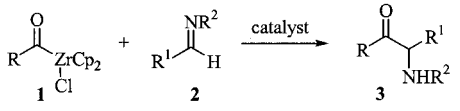
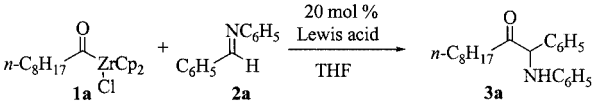
An extension of this reaction behavior of **1** to imine derivatives **2** would be expected to yield α-amino ketone compounds **3** (Scheme 2), which are found in a variety of biologically important molecules,[6] and we have reported a direct route to **3** through Yb(OTf)$_3$/TMSOTf-catalyzed reactions between compounds **1** and *N*-benzylideneaniline derivatives **2** (Scheme 3).[7] This is the first example of the formation of α-amino ketones **3** by nucleophilic attack of "unmasked" acyl groups on imines **2**. In this paper we offer a full account of the formation of α-amino ketones **3** through (i) Lewis and Brønsted acid catalyzed reactions between acylzirconocene chlorides **1** and imines **2**, and (ii) three-component reactions involving aldehydes, anilines, and acylzirconocene chlorides **1**.



Scheme 2



catalyst	**3a** yield (%)	catalyst	**3a** yield (%)
$BF_3•OEt_2$[a]	—	$Yb(OTf)_3$	23[b] (53[c])
$TiCl_4$[a]	—	$Yb(OTf)_3$-TMSOTf (1 : 1)	64
$AlCl_3$[a]	—	$Yb(OTf)_3$-TMSOTf (1 : 5)	51
$Sc(OTf)_3$	22	$Yb(OTf)_3$-TMSCl (1 : 1)	63

[a] a stoichiometric amount. [b] ambient temperature, 72 h. [c] 50 °C, 8 h.

Scheme 3

Results and Discussion

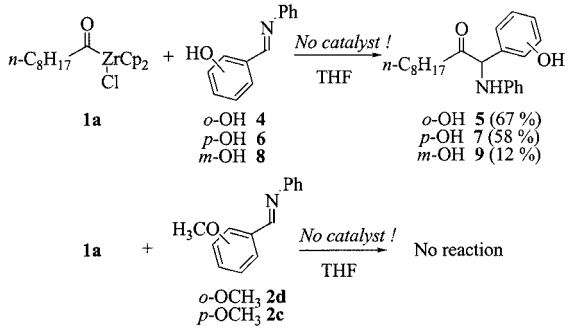
Yb-Catalyzed Reaction

Initially, the nucleophilic reaction between **1** and imine **2** was examined as in the case of the reaction with aldehydes by use of a Lewis acid.[5] However, treatment of nonanoylzirconocene chloride (**1a**) with *N*-benzylideneaniline (**2a**) in the presence of stoichiometric amounts of Lewis acids such as $BF_3{\cdot}OEt_2$, $TiCl_4$, TMSOTf, $AlCl_3$, etc. failed to yield α-amino ketone **3a** (Scheme 3). A recent report[8] on the catalytic activity of lanthanide metal complexes for the activation of imine derivatives in nucleophilic reactions suggested the use of ytterbium triflate [$Yb(OTf)_3$] as a Lewis acid in our attempted reactions of acylzirconocene chlorides. Thus, in the presence of $Yb(OTf)_3$ (20 mol %), treatment of **1a** (1.3 equiv.) with **2a** at ambient temperature in THF proceeded slowly (72 h, by TLC) to produce **3a** in 23% yield. By heating the reaction mixture at 50 °C for 8 h, **3a** was obtained in 53% yield (Scheme 3). Under these heating conditions, however, a longer reaction period (> 8 h) tended to yield a contaminated reaction mixture (by TLC). Recently, the use of $Yb(OTf)_3$/TMSOTf in a 1:1 ratio has been reported to be an efficient catalyst for the activation of imine derivatives.[9] Application of the catalytic system (20 mol %, $Yb(OTf)_3$/TMSOTf, 1:1) in THF to our reaction indicated that treatment of **1a** with **2a** proceeded at ambient temperature over 24 h to give **3a** in 64% yield. The use of a smaller amount of the catalyst (10 mol %) lowered the yield of **3a** (42%). Thus, the $Yb(OTf)_3$/TMSOTf (20 mol %, 1:1) system is preferable to the use of only $Yb(OTf)_3$ as a catalytic system in this reaction. A higher ratio of TMSOTf to $Yb(OTf)_3$ (5:1) turned out to be less efficient. The use of TMSCl as a substitute for TMSOTf produced **3a** in a comparable yield (63%).

The use of scandium triflate [$Sc(OTf)_3$] in place of $Yb(OTf)_3$ as a catalyst showed an efficiency similar to that of $Yb(OTf)_3$. It turned out that, in these $Yb(OTf)_3$/TMSOTf-catalyzed reactions, the employed solvent, THF, is integral to bring about the reaction. The use of a solvent other than THF − such as CH_2Cl_2, CH_3CN, DMF, or DME − retarded the reaction (CH_2Cl_2, CH_3CN) or rendered it complex (DMF or DME; by TLC). We thus believe that $Yb(OTf)_3$/TMSOTf (20 mol %, 1:1) in THF is the catalyst of choice in these reactions. The results from $Yb(OTf)_3$/TMSOTf (20 mol %, 1:1) catalyzed reactions between imine derivatives **2** and acylzirconocene chlorides **1** in THF are listed in Table 1. The $Yb(OTf)_3$/TMSOTf (20 mol %) catalyzed reaction of **1** is restricted to the addition to *N*-benzylideneaniline derivatives, since imine derivatives (**2h** and **2i**) derived from cyclohexanecarbaldehyde or pivalaldehyde with aniline reacted with **1a** to produce products in less than 5% yield (Entries 8 and 9, respectively). The α,β-unsaturated acylzirconocene chloride **1d** yielded a poor amount of product (Entry 12).

Brønsted Acid Catalyzed Reaction

During the study of the reaction between **1** and imines **2**, we observed that treatment of **1a** (1.3 equiv.) with *N*-salicylideneaniline (**4**), which possesses a free *ortho*-phenolic hydroxy group in the benzylidene moiety, proceeded *in the absence of a catalyst* to afford α-amino ketone **5** in 67% yield (Scheme 1). *N*-(*p*-Hydroxybenzylidene)aniline (**6**), a *para* isomer of **4**, also reacted with **1a** to produce α-amino ketone **7** in 58% yield. However, treatment of *N*-(*m*-hydroxybenzylidene)aniline (**8**) with **1a** produced α-amino ketone **9** in only 12% yield. Neither *N*-(*o*-methoxybenzylidene)ani-



Scheme 4. Reactions of *N*-(hydroxybenzylidene)aniline derivatives with **1a**

Table 1. Reactions between compounds **1** and compounds **2** in the presence of $Yb(OTf)_3$/TMSOTf

Entry	**1** R	**2** R^1, R^2	**3** (Yield [%][a])
1	*n*-C_8H_{17} (**1a**)	C_6H_5, C_6H_5 (**2a**)	**3a** (64)
2	**1a**	*p*-$F_3CC_6H_4$, C_6H_5 (**2b**)	**3b** (54
3	**1a**	*p*-$H_3COC_6H_4$, C_6H_5 (**2c**)	**3c** (65)
4	**1a**	*o*-$H_3COC_6H_4$, C_6H_5 (**2d**)	**3d** (37)
5	**1a**	1-naphthyl, C_6H_5 (**2e**)	**3e** (41)
6	**1a**	C_6H_5, *p*-$F_3CC_6H_4$ (**2f**)	**3f** (51)
7	**1a**	C_6H_5, *p*-FC_6H_4 (**2g**)	**3g** (55)
8	**1a**	*c*-C_6H_{11}, C_6H_5 (**2h**)	−
9	**1a**	*t*Bu, C_6H_5 (**2i**)	−
10	*c*-$C_6H_{11}CH_2$ (**1b**)	**2a**	**3h** (59)
11	*t*Bu$(CH_2)_2$ (**1c**)	**2a**	**3i** (41)
12	(*E*)-$C_6H_5(CH_2)_2CH{=}CH$ (**1d**)	**2a**	**3j** (12)

[a] Isolated yield.

line (**2d**) nor *N*-(*p*-methoxybenzylidene)aniline (**2c**) reacted with **1a** to yield any appreciable quantity of product without the use of a catalyst (Scheme 4). Thus, the presence of a free phenolic hydroxy group at the *o*- and *p*-positions of the benzylidene moieties in **4** and **6** served to fill the role of an efficient additive in the reactions. In contrast, the *m*-OH group was less efficient.

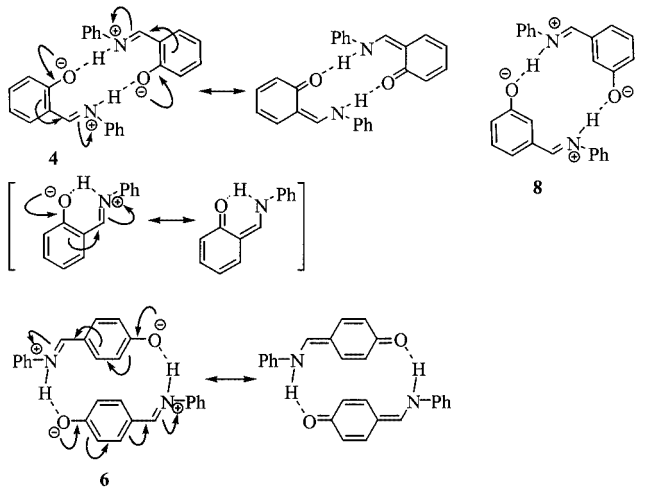
In order to confirm the effect of the phenolic hydroxy groups of **4**, **6**, and **8** on the reaction, **2a** (1.0 equiv.) was treated with **1a** (2.0 equiv.) *in the presence of 1.0 equiv. of phenol derivatives* (Entries 1−3, Table 2).[10] Addition of phenol to a mixture of **1a** and **2a** resulted in the formation of small quantities of **3a** (9% yield, Entry 1). Addition of *p*-nitrophenol or 2,4-dinitrophenol to the mixture in place of phenol afforded a marked increase in the yields of **3a**, to 61 and 78%, respectively (Entries 2 and 3). The reaction also proceeded on use of a catalytic amount (20 mol %) of 2,4-dinitrophenol, which provided **3a** in 62% yield (Entry 4). However, use of a catalytic amount of picric acid resulted in a decreased yield (Entry 5).[11] Additionally, Brønsted acids other than the phenol derivatives − such as CF_3SO_3H,[12] HCl (g), aq. 35% hydrochloric acid, or aq. 50% $HClO_4$ − proved to be efficient catalysts for these purposes (Entries 6−9). It should be noted that even aqueous acid could be employed as a catalyst (Entries 6 and 8) as the ready hydrolysis of acylzirconocene chloride **1** by aqueous acid to aldehyde is well known.[1]

Table 2. Reactions between compounds **1** and compounds **2** in the presence of Brønsted acids

Entry[a]	Brønsted acid (equiv.)	Yield [%] of **3a**[b]
1	C_6H_5OH (1.0)	9
2	*p*-$O_2NC_6H_4OH$ (1.0)	61
3	2,4-$(O_2N)_2C_6H_3OH$ (1.0)	78
4	2,4-$(O_2N)_2C_6H_3OH$ (0.2)	62
5	picric acid (0.2)	24
6	36% aq. HCl (0.2)	70
7	CF_3SO_3H (0.2)	72
8	60% aq. $HClO_4$ (0.2)	55
9	0.5 M HCl in THF (0.2)	80

[a] Ratio of the reagents **1a**/**2a** = 2:1. [b] Isolated yield.

It is worth noting that benzaldehyde does not react with **1a** through the addition of a catalytic or stoichiometric amount of a Brønsted acid. These observations indicate the importance of Brønsted acids with respect to the chemoselective activation of imines **2**. Thus, in the reactions of the *N*-(hydroxybenzylidene)aniline derivatives **4**, **6**, and **8** (Scheme 4), the low reactivity of the *m*-OH isomer **8** might be attributable to a less efficient protonation of the imine portion than obtained with **4** and **6**.[13] Although the exact reason for the low reactivity of the *m*-OH isomer **8** remains unclear, the lack of resonance between the zwitterions and quinoid forms through intermolecular protonation in **8** would explain the inefficiency of the protonation (Scheme 5). In the *o*-OH and *p*-OH isomers **4** and **6**, however, such zwitterionic resonance is possible. This resonance



Scheme 5. Intra- or intermolecular protonation of **4**, **6**, and **8**

would thus contribute to the protonation of the imine functions in **4** and **6** (Scheme 5).

An effect of phenol derivatives in the reaction between **1a** and **2a** suggests that protonation of the imine function by phenol seems insufficient compared to that of *p*-nitrophenol and/or 2,4-dinitrophenol (Entries 1−3, Table 2). Results of 20 mol % HCl (g)/THF (0.5 M solution) catalyzed reactions between compounds **1** and compounds **2** at ambient temperature for 12 h are presented in Table 3. Imine **2h**, derived from cyclohexanecarbaldehyde and aniline, provided the α-amino ketone **3l** in 57% yield (Entry 3, Table 3), this compound having been unobtainable under the previously described $Yb(OTf)_3$/$TMS(OTf)_3$ catalyzed conditions (Entry 8, Table 1). The *t*Bu-substituted imine **2i** did not allow the formation of **3** even under the use of 20 mol % HCl (g)/THF (0.5 M solution) catalyzed conditions (Entry 4), however. The α,β-unsaturated acylzirconocene chloride **1d**, which had been a poor reactant in Yb-catalyzed reactions (Entry 12, Table 1), produced α-amino ketone **3j** in 56% yield (Entry 8, Table 3). Addition of $BF_3{\cdot}OEt_2$ (20 mol %) to the HCl(g)/THF (0.5 M solution, 20 mol %) catalyzed reaction mixture of **1a** and **2a** in THF at 0 °C shortened

Table 3. HCl (0.5 M)/THF catalyzed reactions between compounds **1** and compounds **2**

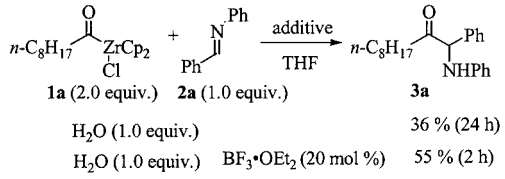
Entry[a]	**1**	**2** R^1, R^2	**3** (Yield [%][b])
1	**1a**	**2c**	**3c** (80)
2	**1a**	*p*-$O_2NC_6H_4$, C_6H_5	**3k** (61)
3	**1a**	**2h**	**3l** (57)
4	**1a**	**2i**	−
5	**1a**	**2a**	**3a** (80 {83[c]})
6	**1b**	**2a**	**3h** (60)
7	**1c**	**2a**	**3i** (58)
8	**1d**	**2a**	**3j** {56[c]}

[a] Ratio of the reagents **1**/**2** = 2:1. [b] Isolated yield. [c] Yield in parentheses is based on 0.2 equiv. use of 0.5 M HCl/THF solution and $BF_3{\cdot}OEt_2$ at ambient temperature for 4 h.

the reaction period from 12 h to 4 h (by TLC, Entries 5 and 8). A highly efficient activation of imine derivatives with Brønsted acids has been reported for reactions between imine derivatives and TMS-enolate nucleophiles.[14,15]

Three-Component Reaction

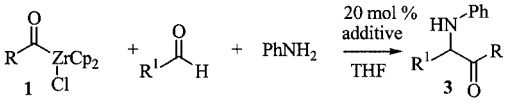
Interestingly, addition of H_2O (1.0 equiv.) instead of the Brønsted acid to a mixture of **1a** (2.0 equiv.) and **2a** (1.0 equiv.) in THF at ambient temperature for 24 h afforded a significant amount of **3a** (36% yield, Scheme 6).[16] Furthermore, addition of $BF_3{\cdot}OEt_2$ (20 mol %) to the reaction mixture shortened the reaction time (2 h) and increased the yield of **3a** to 55%.



Scheme 6

As no reaction had occurred when $BF_3{\cdot}OEt_2$ had been used under anhydrous conditions, the acceleration by $BF_3{\cdot}OEt_2$ is regarded as a result of the formation of a very active Brønsted acid, such as $H^+BF_3X^-$ (X = OH and/or Cl), from $BF_3{\cdot}OEt_2$ and H_2O and/or HCl generated in situ. The formation of $H^+BF_3X^-$ from $BF_3{\cdot}OEt_2$ and H_2O has been suggested by Akiyama et al.[15d]

The generation of imine compounds from aldehydes and amines necessarily produces 1 equiv. of H_2O in the reaction media. It was thus thought plausible that the direct formation of α-amino ketones **3** by treatment of aldehydes, anilines, and acylzirconocene chlorides **1** in a single pot (the so-called three-component synthesis) should be possible (Scheme 7).[17] The assumption proved to be correct, and the results of three-component reactions between compounds **1**, aldehydes, and anilines are listed in Table 4.



Scheme 7

The one-pot reaction between benzaldehyde (1.0 equiv.), aniline (1.0 equiv.), and **1a** (2.0 equiv.) reached completion within 7 h at ambient temperature in THF, affording **3a** in 72% yield (Entry 1). Addition of molecular sieves (4 Å) or $MgSO_4$ to the mixture of **1a**, benzaldehyde, and aniline retarded the formation of **3a**. As anticipated from the results shown in Scheme 6, addition of Lewis acid [20 mol %, $BF_3{\cdot}OEt_2$ or $Yb(OTf)_3$][18] or Brønsted acid catalyst to the three-component reaction mixture shortened the reaction times to 2 h with comparable or even higher yields of **3** (Entries 2−12). We had previously reported the formation of α-ketols through $BF_3{\cdot}OEt_2$-mediated reactions between **1** and aldehydes.[5] Under these $BF_3{\cdot}OEt_2$-accelerated three-component reactions, however, α-ketols were not detected.

Table 4. Three-component syntheses of compounds **3**

Entry[a]	**1**	Aldehyde R^1	Additive	**3** (Yield [%][b])
1	**1a**	C_6H_5	−	**3a** (72)
2	**1a**	C_6H_5	$BF_3{\cdot}OEt_2$	**3a** (60)
3	**1a**	C_6H_5	$Yb(OTf)_3$	**3a** (81)
4	**1a**	C_6H_5	60% $HClO_4$	**3a** (67)
5	**1a**	C_6H_5	HCl (g)/THF[c]	**3a** (55)
6	**1a**	*p*-$H_3COC_6H_4$	$BF_3{\cdot}OEt_2$	**3c** (55)
7	**1a**	*p*-$H_3COC_6H_4$	$Yb(OTf)_3$	**3c** (81)
8	**1a**	*p*-$O_2NC_6H_4$	$BF_3{\cdot}OEt_2$	**3k** (55)
9	**1a**	*p*-$O_2NC_6H_4$	$Yb(OTf)_3$	**3k** (78)
10	**1a**	*c*-C_6H_{11}	$Yb(OTf)_3$	**3l** (83)
11	**1b**	C_6H_5	$Yb(OTf)_3$	**3h** (70)
12	**1d**	C_6H_5	$Yb(OTf)_3$	**3j** (43)

[a] Ratio of the reagents **1**/aldehyde/aniline = 2:1:1. [b] Isolated yield. [c] 0.5 M solution in THF.

Conclusion

The nucleophilic addition of "unmasked" acyl anions to *N*-benzylideneaniline derivatives was achieved under Lewis acid catalyzed anhydrous conditions or Brønsted acid catalyzed conditions, even including the use of aqueous acid. Furthermore, a logical extension of the experiment resulted in the direct formation of α-amino ketones by the three-component reaction. The three-component reaction is more efficient, not only with respect to operational simplicity but also in terms of higher yields of α-amino ketones, than that between imines and acylzirconocene chloride. The three-component synthesis of amines from aldehydes, amines, and nucleophiles is attractive, owing to its operational simplicity and the ready preparation of a library of small molecules.[17] The results described here show the further utility of acylzirconocene chlorides as "unmasked" acyl anion donors in organic synthesis.

Experimental Section

General Remarks: All nonaqueous reactions were carried out under argon. Anhydrous solvents (diethyl ether, THF, and CH_2Cl_2) and reagents other than $Cp_2Zr(H)Cl$ were obtained from commercial suppliers and used without further purification. The Schwartz reagent [$Cp_2Zr(H)Cl$] was prepared by the procedure reported by Buchwald et al.[19] Starting imines were purchased (**2a**) or prepared (**2b**−**g**, **4**, **6**, and **8**) by an established procedure.[20] Product **3** was isolated from a crude reaction mixture by silica gel column chromatography, with hexanes/ethyl acetate (80:1) as an eluting solvent. Further purification, if necessary, was carried out by medium pressure column chromatography (prepacked column) with the same

solvent system. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz, respectively. The described yields (isolated) and weights of products **3a**−**3j** are based on the results of the $Yb(OTf)_3$/TMSOTf-catalyzed reactions shown in Table 1.

Preparation of THF Solutions of Compounds 1: A suspension of $[Cp_2Zr(H)Cl]$ (1.0 equiv.) and the alkene or alkyne (2.0 equiv.) in CH_2Cl_2 (4.0 mL/mmol) was stirred at ambient temperature for 0.5 h and the mixture was treated with carbon monoxide for 2 h (CO balloon). After the CH_2Cl_2 had been removed in vacuo, THF (8.0 mL/mmol) was added to the residue.

$Yb(OTf)_3$/TMSOTf-Catalyzed Formation of Compounds 3: A solution of imine derivative **2** (1.0 mmol, 1.0 equiv.), $Yb(OTf)_3$, and TMSOTf (20 mol %) in THF (3.0 mL/mmol) was added at 0 °C to a solution of **1** (1.3 equiv.) in THF (8.0 mL/mmol), and the mixture was stirred at ambient temperature for 24 h. The reaction mixture was treated with saturated aq. $NaHCO_3$ (ice cooling) and extracted with ethyl acetate. The combined organic layers were washed with brine, dried with $MgSO_4$, and filtered. The filtrate was concentrated to dryness to yield crude product **3**.

Brønsted Acid Catalyzed Formation of 3: A solution of HCl(g)/THF (0.5 M, 0.2 equiv.) was introduced at 0 °C to a solution of **1** (2.0 equiv.) and **2** (1.0 mmol, 1.0 equiv.) in THF (10.0 mL/mmol). The mixture was subsequently stirred at ambient temperature for 12 h. Workup and purification as described above yielded **3**.

Lewis Acid Accelerated Three-Component Synthesis of 3: A premixed solution (0.5 h at ambient temperature) of aldehyde (1.0 mmol, 1.0 equiv.) and aniline (1.0 equiv.) in THF (6.0 mL/mmol) was added to a solution of **1** (2.0 equiv.) in THF (8.0 mL/mmol) at 0 °C. A solution of $Yb(OTf)_3$ or $BF_3{\cdot}OEt_2$ (0.2 equiv.) in THF (1.0 mL) at 0 °C was introduced to the resulting mixture, and it was stirred for 2 h at ambient temperature. Workup and purification as described above yielded **3**.

1-Phenyl-1-(phenylamino)-2-decanone (3a): Yield 64% (207 mg); m.p. 59−61 °C. IR (KBr): $\tilde{\nu}$ = 3387, 2921, 1709, 1603 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.0 Hz, 3 H), 1.14−1.38 (m, 10 H), 1.38−1.60 (m, 2 H), 2.35−2.48 (m, 2 H), 4.98 (d, *J* = 3.0 Hz, 1 H), 5.47 (d, *J* = 3.8 Hz, 1 H), 6.54 (d, *J* = 7.6 Hz, 2 H), 6.64 (t, *J* = 7.3 Hz, 1 H), 7.06−7.08 (m, 2 H), 7.27−7.45 (m, 5 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.0, 22.6, 23.8, 28.9, 29.0, 29.1, 29.6, 31.7, 39.1, 67.6, 113.3, 117.5, 127.8, 128.2, 129.1, 138.1, 146.0, 206.4 ppm. EIMS: *m*/*z* = 323 [M^+]. $C_{22}H_{29}NO$ (323.47): calcd. 323.224915; found 323.223747 (HRMS).

1-(Phenylamino)-1-[4-(trifluoromethyl)phenyl]-2-decanone (3b): Yield 54% (211 mg); m.p. 54−56 °C. IR (KBr): $\tilde{\nu}$ = 3387, 1699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.0 Hz, 3 H), 1.13−1.28 (m, 10 H), 1.46−1.55 (m, 2 H), 2.33−2.42 (ddd, *J* = 6.9, 7.9, 17.0 Hz, 1 H), 2.43−2.51(ddd, *J* = 6.4, 8.2, 17.0 Hz, 1 H), 5.05 (d, *J* = 4.2 Hz, 1 H), 5.50 (d, *J* = 4.1 Hz, 1 H), 6.50 (d, *J* = 7.8 Hz, 2 H), 6.67 (t, *J* = 7.3 Hz, 1 H), 7.07−7.12 (m, 2 H), 7.58−7.64 (m, 4 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.0, 22.6, 23.8, 28.9, 29.0, 29.1, 31.7, 39.3, 67.3, 113.3, 118.0, 122.5, 125.2, 126.1, 126.2, 128.2, 129.3, 130.4, 130.8, 142.5, 145.6, 205.3 ppm. EIMS: *m*/*z* = 391 [M^+]. $C_{23}H_{28}F_3NO$ (391.47): calcd. C 70.57, H 7.21, N 3.58; found C 70.57, H 7.02, N 3.50.

1-[4-(Methoxy)phenyl]-1-(phenylamino)-2-decanone (3c): Yield 65% (230 mg); m.p. 79−80 °C. IR (KBr): $\tilde{\nu}$ = 3389, 2851, 1700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.0 Hz, 3 H), 1.16−1.29 (m, 10 H), 1.40−1.57 (m, 2 H), 2.35−2.48 (t, *J* = 7.3 Hz, 2 H), 3.79 (s, 3 H), 4.94 (d, *J* = 2.6 Hz, 1 H), 5.43 (d, *J* = 2.5 Hz, 1 H), 6.55 (d, *J* = 7.7 Hz, 2 H), 6.65 (t, *J* = 7.3 Hz, 1 H), 6.88−6.90 (dt, *J* = 2.4, 9.6 Hz, 2 H), 7.07−7.36 (m, 4 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.0, 22.6, 23.9, 28.9, 29.0, 29.1, 31.7, 39.0, 55.2, 66.9, 113.3, 114.5, 117.5, 129.0, 129.1, 129.9, 146.1, 160.0, 206.7 ppm. EIMS: *m*/*z* = 353 [M^+]. $C_{23}H_{31}NO_2$ (353.50): calcd. C 78.15, H 8.84, N 3.96; found C 78.23, H 8.68, N 3.95.

1-[2-(Methoxy)phenyl]-1-(phenylamino)-2-decanone (3d): Yield 37% (130 mg); m.p. 40−42 °C. IR (KBr): $\tilde{\nu}$ = 3392, 2928, 1710 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.0 Hz, 3 H), 1.19−1.33 (m, 10 H), 1.45−1.63 (m, 2 H), 2.34−2.42 (ddd, *J* = 7.1, 7.9, 16.5 Hz, 1 H), 2.44−2.51 (ddd, *J* = 6.4, 8.2, 16.5 Hz, 1 H), 4.02 (t, *J* = 12.6 Hz, 3 H), 5.44 (d, *J* = 4.1 Hz, 1 H), 5.61 (d, *J* = 4.8 Hz, 1 H), 6.57 (d, *J* = 7.8 Hz, 2 H), 6.66 (t, *J* = 7.3 Hz, 1 H), 6.91−7.31 (m, 6 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.0, 22.6, 23.9, 28.9, 29.0, 29.1, 31.7, 38.9, 55.6, 59.8, 110.7, 113.0, 117.2, 121.3, 126.1, 128.2, 129.0, 129.2, 146.2, 157.0, 206.8 ppm. EIMS: *m*/*z* = 353 [M^+]. $C_{23}H_{31}NO_2$ (353.50): calcd. C, 78.15, H 8.84, N 3.96; found C 78.15, H 8.57, N 3.85.

1-(1-Naphthalenyl)-1-(phenylamino)-2-decanone (3e): Yield 41% (153 mg); m.p. 63−65 °C. IR (neat): $\tilde{\nu}$ = 3300, 2925, 1716 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.2 Hz, 3 H), 1.04−1.60 (m, 12 H), 2.25−2.31 (ddd, *J* = 6.8, 8.0, 14.8 Hz, 1 H), 2.41−2.47 (ddd, *J* = 6.3, 8.2, 16.9 Hz, 1 H), 5.63 (d, *J* = 3.4 Hz, 1 H), 5.73 (d, *J* = 3.4 Hz, 1 H), 6.62 (d, *J* = 7.8 Hz, 2 H), 6.68 (t, *J* = 7.3 Hz, 1 H), 7.07−7.11 (dd, *J* = 7.5, 8.3 Hz, 2 H), 7.55−7.68 (m, 4 H), 7.86 (d, *J* = 8.2 Hz, 1 H), 7.94 (m, 1 H), 8.37 (d, *J* = 8.5 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.5, 23.0, 24.3, 29.2, 29.3, 29.5, 32.1, 39.6, 65.2, 113.8, 118.1, 123.4, 126.1, 126.3, 127.3, 129.5, 129.6, 129.7, 131.8, 134.3, 134.8, 146.9, 207.3 ppm. EIMS: *m*/*z* = 373 [M^+]. $C_{26}H_{31}NO$ (373.53): calcd. C 83.60, H 8.37, N 3.75; found C 83.56, H 8.09, N 3.55.

1-Phenyl-1-[(4-trifluoromethylphenyl)amino]-2-decanone (3f): Yield 51% (200 mg); m.p. 75−78 °C. IR (KBr): $\tilde{\nu}$ = 3393, 2925, 1700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.0 Hz, 3 H), 1.15−1.28 (m, 10 H), 1.41−1.55 (m, 2 H), 2.36−2.47 (m, 2 H), 5.00 (d, *J* = 4.5 Hz, 1 H), 5.85 (d, *J* = 4.1 Hz, 1 H), 6.54 (q, *J* = 8.5 Hz, 2 H), 7.29−7.43 (m, 7 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.0, 22.6, 23.8, 28.9, 29.0, 29.1, 31.7, 39.1, 66.9, 112.6, 124.8, 126.4, 127.8, 128.6, 129.3, 137.2, 148.3, 205.5 ppm. EIMS: *m*/*z* = 391 [M^+]. $C_{23}H_{28}F_3NO$ (391.46): calcd. C 70.57, H 7.21, N 3.58; found C 70.73, H 7.29, N 3.46.

1-[(4-Fluorophenyl)amino]-1-phenyl-2-decanone (3g): Yield 55% (188 mg); m.p. 42−44 °C. IR (KBr): $\tilde{\nu}$ = 3378, 2925, 1706 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 7.0 Hz, 3 H), 1.11−1.29 (m, 10 H), 1.39−1.53 (m, 2 H), 2.33−2.47 (m, 2 H), 4.92 (d, *J* = 4.3 Hz, 1 H), 5.35 (d, *J* = 4.1 Hz, 1 H), 6.43−6.48 (q, *J* = 4.5 Hz, 2 H), 6.75−6.81 (t, *J* = 8.7 Hz, 2 H), 7.28−7.43 (m, 5 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.0, 22.6, 23.9, 28.9, 29.0, 29.1, 31.7, 39.0, 68.2, 114.0, 114.1, 115.4, 115.7, 127.6, 128.3, 129.2, 138.0, 142.4, 154.7, 157.0, 206.3 ppm. EIMS: *m*/*z* = 341 [M^+]. $C_{22}H_{28}FNO$ (341.46): calcd. C 77.38, H 8.27, N 4.10; found C 77.29, H 8.34, N 4.02.

3-Cyclohexyl-1-phenyl-1-(phenylamino)-2-propanone (3h): Yield 59% (181 mg); m.p. 110−112 °C. IR (KBr): $\tilde{\nu}$ = 3382, 2954, 1706, 1604 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.63−0.67 (qd, *J* = 3.0, 12.0 Hz, 1 H), 0.88−0.94 (qd, *J* = 3.2, 11.7 Hz, 1 H), 1.10−1.24 (m, 3 H), 1.43 (d, *J* = 12.8 Hz, 1 H), 1.56−1.82 (m, 5 H), 2.23−2.29 (dd, *J* = 7.2, 16.1 Hz, 1 H), 2.34−2.40 (dd, *J* = 6.5, 16.1 Hz, 1 H), 4.97 (d, *J* = 3.0 Hz, 1 H), 5.51 (d, *J* = 3.1 Hz, 1 H),

6.56−6.68 (m, 3 H), 7.08−7.46 (m, 7 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 25.8, 25.9, 26.0, 32.6, 33.1, 33.9, 68.0, 113.3, 117.5, 127.9, 128.2, 129.0, 129.1, 137.9, 146.0, 205.7 ppm. EIMS: *m/z* = 307 [M^+]. $C_{21}H_{25}NO$ (307.43): calcd. 307.193612; found 307.193605 (HRMS).

5,5-Dimethyl-1-phenyl-1-(phenylamino)-2-hexanone (3i): Yield 41% (120 mg); m.p. 113−115 °C. IR (KBr): ṽ = 3395, 2922, 1708, 1603 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.78 (s, 9 H), 1.20−1.28 (ddd, *J* = 9.9, 13.7, 16.3 Hz, 1 H), 1.45−1.53 (ddd, *J* = 9.0, 13.7, 16.3 Hz, 1 H), 2.35−2.45 (m, 2 H), 5.03 (d, *J* = 4.2 Hz, 1 H), 5.48 (d, *J* = 3.5 Hz, 1 H), 6.56 (d, *J* = 7.9 Hz, 2 H), 6.65 (t, *J* = 7.4 Hz, 1 H), 7.09 (t, *J* = 8.0 Hz, 2 H), 7.28−7.51 (m, 5 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 28.9, 29.9, 34.9, 37.7, 67.6, 76.6, 77.0, 77.3, 113.5, 127.8, 128.3, 129.1, 138.2, 146.0, 206.9 ppm. EIMS: *m/z* = 293 [M^+]. $C_{20}H_{23}NO$ (293.17): calcd. 293.177965; found 293.177955 (HRMS).

1,6-Diphenyl-1-(phenylamino)-hex-3-ene-2-one (3j): Yield 12% (41 mg); m.p. 87−88 °C. IR (KBr): ṽ = 3391, 3025, 2924, 1693 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.45−2.51 (q, *J* = 7.2 Hz, 2 H), 2.72 (t, *J* = 7.2 Hz, 2 H), 5.10 (d, *J* = 3.7 Hz, 1 H), 5.46 (Br. s, 1 H), 6.24 (d, *J* = 15.5 Hz, 1 H), 6.57 (d, *J* = 8.2 Hz, 2 H), 6.66 (t, *J* = 7.3 Hz, 1 H), 7.03−7.43 (m, 13 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 34.1, 66.4, 113.3, 117.6, 126.2, 126.3, 128.1, 128.2, 128.3, 128.7, 129.1, 137.8, 140.5, 146.1, 148.3, 194.6 ppm. EIMS: *m/z* = 341 [M^+]. $C_{24}H_{23}NO$ (341.44): calcd. 341.177965; found 341.179878 (HRMS).

1-(2-Hydroxyphenyl)-1-(phenylamino)-2-decanone (5): Yield 67% (227 mg); m.p. 63−64 °C. IR (KBr): ṽ = 3451, 3272, 1650 cm^{-1}. H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.0 Hz, 3 H), 1.17−1.54 (m, 12 H), 2.37−2.47 (m, 2 H), 4.93 (s, 1 H), 5.47 (s, 1 H), 6.75−6.99 (m, 5 H), 7.14−7.40 (m, 4 H), 8.38 (s, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.0, 22.5, 23.8, 28.8, 28.9, 29.1, 31.7, 38.2, 68.1, 115.9, 117.5, 120.5, 120.7, 121.7, 129.2, 129.8, 130.0, 145.7, 156.5, 206.1 ppm. EIMS: *m/z* = 339 [M^+]. $C_{22}H_{29}NO_2$ (339.47): calcd. C 77.84, H 8.61, N 4.13; found C 77.89, H 8.48, N 4.02.

1-(3-Hydroxyphenyl)-1-(phenylamino)-2-decanone (9): Yield 12% (41 mg); m.p. 73−75 °C. IR (KBr): ṽ = 3396, 2925, 1713, 1602 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.0 Hz, 3 H), 1.16−1.53 (m, 12 H), 2.39−2.48 (m, 2 H), 4.94 (s, 1 H), 5.00 (s, 1 H), 5.42 (s, 1 H), 6.54 (d, *J* = 8.5 Hz, 2 H), 6.66 (t, *J* = 7.3 Hz, 1 H), 6.77 (m, 1 H), 6.88 (t, *J* = 2.0 Hz, 1 H), 7.04−7.11 (m, 3 H), 7.26 (t, *J* = 7.9 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.4, 23.0, 24.2, 29.3, 29.4, 29.5, 32.1, 39.5, 67.8, 113.8, 114.7, 115.9, 118.1, 120.8, 129.5, 130.7, 140.3, 146.3, 156.8, 207.3 ppm. EIMS: *m/z* = 339 [M^+]. $C_{22}H_{29}NO_2$ (339.47): calcd. 339.219829; found 339.218882 (HRMS).

1-(4-Hydroxyphenyl)-1-(phenylamino)-2-decanone (7): Yield 58% (197 mg). IR (KBr): ṽ = 3251, 1647 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 7.0 Hz, 3 H), 1.15−1.52 (m, 12 H), 2.38 (t, *J* = 7.3 Hz, 2 H), 4.86 (s, 1 H), 4.92 (d, *J* = 4.1 Hz, 1 H), 5.40 (d, *J* = 3.9 Hz, 1 H), 6.54−6.83 (m, 5 H), 7.06−7.30 (m, 4 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.5, 23.0, 24.3, 29.3, 29.4, 29.6, 32.1, 39.5, 67.3, 113.7, 116.4, 117.9, 129.5, 129.6, 130.6, 146.5, 155.9, 207.1 ppm. EIMS: *m/z* = 339 [M^+]. $C_{22}H_{29}NO_2$ (339.47): calcd. 339.219829; found 339.219144 (HRMS).

1-(4-Nitrophenyl)-1-(phenylamino)-2-decanone (3k): Yield 61% (112 mg); m.p. 76−77 °C. IR (KBr): ṽ = 3389, 2925, 1699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.0 Hz, 3 H), 1.16−1.62 (m, 12 H), 2.33−2.41 (ddd, *J* = 6.7, 8.0, 17.0 Hz, 1 H), 2.45−2.53 (ddd, *J* = 6.3, 8.3, 17.0 Hz, 1 H), 5.11 (d, *J* = 4.0 Hz, 1 H), 5.52 (d, *J* = 3.8 Hz, 1 H), 6.45 (d, *J* = 7.6 Hz, 2 H), 6.64 (t, *J* = 14.6 Hz, 1 H), 7.06−7.08 (m, 2 H), 7.21−7.45 (m, 5 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.0, 22.6, 23.7, 28.8, 28.9, 29.1, 31.7, 39.5, 67.2, 113.3, 118.3, 124.4, 128.7, 129.3, 145.2, 145.9, 147.9, 204.4 ppm. EIMS: *m/z* = 368 [M^+]. $C_{22}H_{28}N_2O_3$ (368.47): calcd. C 71.71, H 7.66, N 7.60; found C 71.63, H 7.48, N 7.59.

1-Cyclohexyl-1-(phenylamino)-2-decanone (3l): Yield 57% (81 mg); m.p. 36−37 °C. IR (KBr): ṽ = 3386, 2922, 1707 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3 H), 1.15−1.31 (m, 15 H), 1.55 (t, *J* = 7.1 Hz, 2 H), 1.67−1.83 (m, 6 H), 2.38−2.55 (m, 2 H), 3.82 (t, *J* = 5.9 Hz, 1 H), 4.00 (d, *J* = 6.0 Hz, 1 H), 6.95−7.18 (m, 5 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.0, 22.5, 23.3, 26.0, 26.1, 26.2, 28.5, 29.0, 29.1, 29.2, 30.3, 31.7, 40.1, 40.8, 113.2, 117.7, 129.3, 147.8, 212.5 ppm. EIMS: *m/z* = 329 [M^+]. $C_{22}H_{35}NO$ (329.52): calcd. C 80.19, H 10.71, N 4.25; found C 80.10, H 10.66, N 4.23.

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