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Simple and Efficient Methods of Synthesis of 3,3-Diarylcyclobutanone and 3,3-Diarylcyclobutylamine Derivatives Using the $TiCl_4/R_3N$ Reagent System

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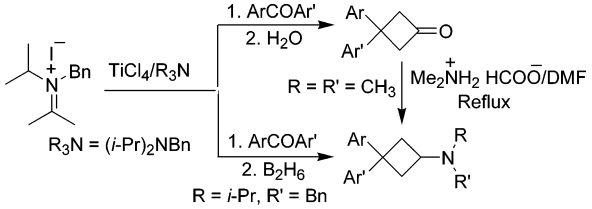

The iminium ions generated in situ by the oxidation of *N,N*-diisopropyl-*N*-benzylamine using iodine react with diaryl ketones in the presence of $TiCl_4/R_3N$ to give the corresponding 3,3-diarylcyclobutanones in moderate to good yields (49−86%). The 3,3-diarylcyclobutanone iminium ions formed in this transformation was reduced in situ with B_2H_6 to produce the corresponding 3,3-diarylcyclobutylamines (52−79% yields), a class of compounds with potential antidepressant activity. In addition, a series of *N,N*-dimethyl-3,3-diarylcyclobutylamines were synthesized by the reductive amination of the corresponding 3,3-diarylcyclobutanone derivatives.

Introduction

Several functionalized cyclobutane derivatives have been shown to possess significant biological activity.[1] For example, certain 3,3-diphenylcyclobutylamine derivatives exhibit antidepressant activity.[2] Accordingly, the corresponding synthons containing cyclobutyl moieties are useful intermediates for the construction of a wide variety of biologically active carbocyclic compounds.[3] Hence, development of a simple and efficient methodology for the synthesis of these functionalized cyclobutyl (cyclobutanones and cyclobutylamines) derivatives from readily available starting materials such as diaryl ketones should be useful. Previously, synthesis of such cyclobutanone derivatives have been reported via methods such as the 2 + 2 cycloaddition of ketenes to olefins,[4] ring enlargement of cyclopropanones formed by addition of diazomethane to ketenes,[5] the 2 + 2 cycloaddition of dichloroketene to olefins,[6] the 2 + 2 cycloaddition of keteniminium salts to olefins,[7] and the condensation of aldehydes and ketones with diphenylsulfonium cyclopropylide followed by acid treatment.[8] Recently, a review covering methods of synthesis of cyclobutanones and their precursors has been published.[9] Herein, we describe the syntheses of 3,3-diarylcyclobutanone and 3,3-diarylcyclobutylamine derivatives by the $TiCl_4/R_3N$-promoted reaction of iminium ions with diaryl ketones.

Results and Discussion

Synthesis of Cyclobutanone Derivatives via 1,3-Dimetalation of Iminium Ions with $TiCl_4/R_3N$ Re-

(1) (a) Cyclobut-A and related antiviral compounds: Norbeck, D. W.; Kern, E.; Hayashi, S.; Rosenbrook, W.; Sham, H.; Herrin, T.; Plattner, J. J.; Erickson, J.; Clement, J.; Swanson, R.; Shipkowitz, N.; Hardy, D.; Marsh, K.; Arnett, G.; Shannon W.; Broder, S.; Mitsuya, H. *J. Med. Chem*. **1990**, *33*, 1281. (b) Brown, B.; Hegedus, L. S. *J. Org. Chem*. **1998**, *63*, 8012 and references cited therein. (c) Friesen, R. W.; Dube, D.; Fortin, R.; Frenette, R.; Prescott, S.; Cromlish, W.; Greig, G. M.; Kargman, S.; Wong, E.; Chan, C. C.; Gordon, R.; Xu, L. J.; Rideneau, D. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 2677. (d) Delincee, H.; PoolZobel, B. L. *Radiat. Phys. Chem*. **1998**, *52*, 39.

(2) Carnmalm, B.; Ramsby, S.; Renyi, A. L.; Ross, S. B.; Ogren, S.-O.; Stjernstrom, N. E. *J. Med. Chem*. **1978**, *21*, 78.

(3) (a) Bellus, D.; Ernst, B. *Angew. Chem., Int. Ed. Engl*. **1988**, *27*, 797. (b) Nemoto, H.; Fukumoto, K. *Synlett* **1997**, 863. (c) Adam, J. M.; Ghosez, L.; Houk, K. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2728. (d) Brown, R. C. D.; Hinks, J. D. *J. Chem. Soc., Chem. Commun*. **1998**, 1895. (e) Lee-Ruff, E.; Ostrowski, M.; Ladha, A.; Stynes, D. V.; Vernik, I.; Jiang, J. L.; Wan, W. Q.; Ding, S. F.; Joshi, S. *J. Med. Chem*. **1996**, *39*, 5276.

(4) Marvel, C. S.; Kohan, M. I. *J. Org. Chem*. **1951**, *16*, 741.

(5) Michejda, C. J.; Comnick, R. W. *J. Org. Chem.* **1975**, *40*, 1046.

(6) Krepski, L. R.; Hassner, A. *J. Org. Chem.* **1978**, *43*, 2879.

(7) Sidani, A.; Marchand-Brynaert, J.; Ghosez, L. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 267.

(8) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5321 and references cited there in.

(9) Salaun, J. *Scie. Synth.* **2004**, *26*, 557.

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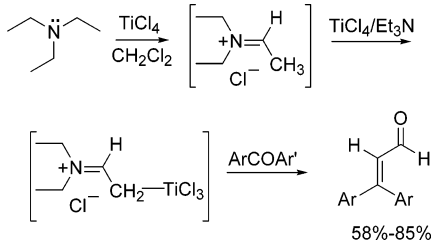
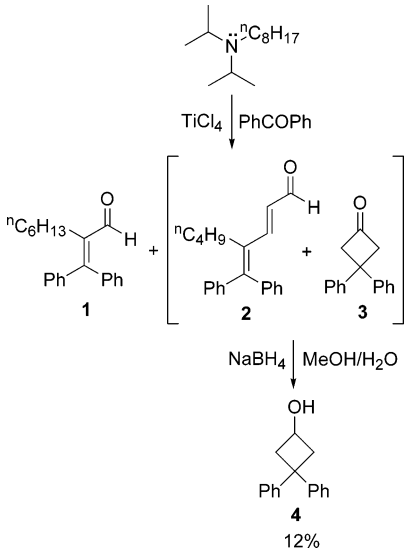
SCHEME 1. Synthesis of α,β-Unsaturated Aldehydes

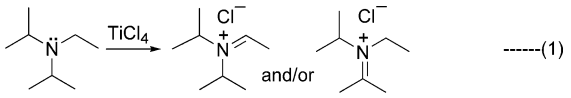


SCHEME 2. Reaction of *N,N*-Diisopropyl-*N*-octylamine with $TiCl_4$/PhCOPh



agent System.[10] It has been previously reported from this laboratory that the iminium ions formed in situ by the reaction of trialkylamines by $TiCl_4$ readily react with diaryl ketones to give the corresponding α,β-unsaturated aldehydes (Scheme 1).[11]

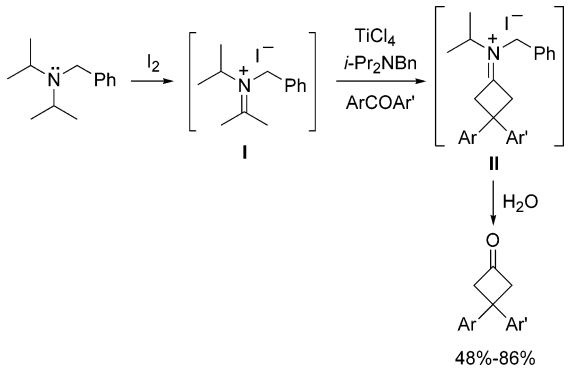
It was of interest to examine the reaction of the iminium ions produced in situ using *N,N*-diisopropyl-*N*-ethylamine (eq 1).



Interestingly, in this case, the product mixture showed the presence of a cyclobutanone derivative **3** (IR 1790 cm^{-1}) besides the corresponding α,β-unsaturated aldehyde. However, the product mixture was obtained only in very small amounts. The use of *N,N*-diisopropyl-*N*-octylamine produced the product mixture from which the corresponding cyclobutanol **4** could be readily separated after reduction of the product mixture of **2** and **3** with $NaBH_4-MeOH-H_2O$ (overall yield 12%) (Scheme 2).

Efforts undertaken to optimize the reaction conditions using other amines such as *N,N*-diisopropyl-*N*-methylamine also gave poor results. Therefore, we have examined the use of iminium ions prepared using other methods in the reaction with $TiCl_4$/PhCOPh/R_3N.

SCHEME 3. One-Pot Synthesis of 3,3-Diarylcyclobutanone Derivatives



Previously, it was reported that the iminium ions and enamines are generated from the oxidation of tertiary amines by iodine.[12] The iminium ion prepared from the oxidation of *N,N*-diisopropyl-*N*-methylamine by iodine was reacted with $TiCl_4$/*N,N*-diisopropyl-*N*-methylamine/benzophenone. However, the corresponding cyclobutanone derivative was obtained only in very low yield (4%). The use of other tertiary amines such as *N*-isopropylpiperidine and *N,N*-dimethyl-*N*-isopropylamine for the preparation of iminium ions using iodine, followed by the reaction with $TiCl_4$/corresponding tertiary amine/benzophenone did not give the expected cyclobutanone derivative. Fortunately, in the reaction of iminium ions with $TiCl_4$/*N,N*-diisopropyl-*N*-benzylamine and benzophenone the corresponding cyclobutanone derivative was obtained in 76% yield (Scheme 3).

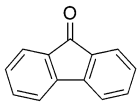
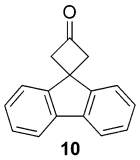
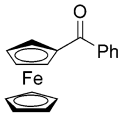
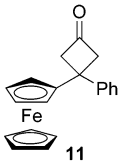
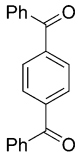
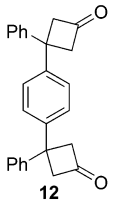
This transformation was examined using several diaryl ketones, and the results are summarized in Table 1. We have carried out several experiments to examine the scope and limitations of this transformation. Initially, the reaction was carried out at 25 °C after the addition of $TiCl_4$ to the iminium ions at 0 °C. It was found that the yields of cyclobutanone are slightly better (10−20% more) under refluxing conditions. Dichloroethane was found to be the best solvent compared to CH_2Cl_2 and $CHCl_3$ under these reaction conditions. The yields are optimum when 2 equiv of tertiary amine was oxidized using 1 equiv of iodine and the iminium iodide was reacted with 3 equiv of $TiCl_4$ and tertiary amine and 1 equiv of the diaryl ketone. It was found that the second addition of tertiary amine is needed for the reaction of the iminium ions without which the cyclobutanone was not formed. The use of TMEDA instead of *N,N*-diisopropyl-*N*-benzylamine for the reaction of the iminium ion gave the cyclobutanone derivative in poor yields (6%).

It was reported that in the presence of excess trialkylamine the iodine oxidation of trialkylamine produces enamines.[12] To examine whether such enamine intermediates could react with diaryl ketone to produce the corresponding cyclobutanone derivatives, we have carried out experiments without using $TiCl_4$. However, the cyclobutanone derivative was not formed in the absence of $TiCl_4$.

To examine the generality of this methodology, the reaction of iminium ion intermediate **I** was carried out

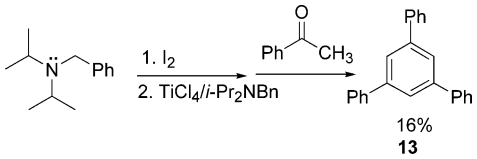
(10) Periasamy, M.; Jayakumar, K. N.; Bharathi, P. *Chem. Commun*. **2001**, 1728.
(11) Bharathi, P.; Periasamy, M. *Org. Lett*. **1999**, *1*, 857.
(12) Wadsworth, D. H.; Detty, M. R.; Murray, B. J.; Weidner, C. H.; Haley, N. F. *J. Org. Chem*. **1984**, *49*, 2676 and references therein.

TABLE 1. Reaction of Iminium Ions with $TiCl_4/R_3N$ and Diaryl Ketones

Entry	Substrate	Product[a]	Yield[b] %
1	Ar=Ar'=Ph	**5**	76
2	Ar=Ar'=4-ClC_6H_4	**6**	86
3	Ar=Ar'=4-$CH_3C_6H_4$	**7**	71
4	Ar=Ar'=4-FC_6H_4	**8**	80
5	Ar=Ph, Ar'=4-$CH_3C_6H_4$	**9**	73
6		**10** 	58
7		**11** 	51
8		**12** 	49

[a] The products were identified by ^1H and ^{13}C NMR and mass spectral data. [b] The yields are based on the diaryl ketone used.

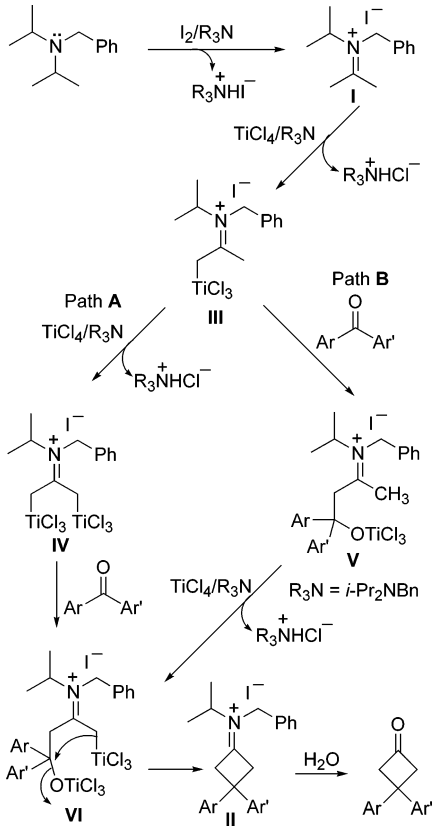
SCHEME 4. Reaction of Acetophenone with Iminium Ion I/$TiCl_4$/*i*-Pr_2NBn



with $TiCl_4$/*N,N*-diisopropyl-*N*-benzylamine/arylalkyl ketones or dialkyl ketones. The reaction of acetophenone with **I**/$TiCl_4$/*N,N*-diisopropyl-*N*-benzylamine gave a complex mixture of products in addition to the triple self-condensation product of acetophenone, 1,3,5-triphenylbenzene **13** in 16% yield (Scheme 4). Recently, it has been reported that such triple self-condensation of ketones is promoted by titanium tetrachloride[13] and also by $TiCl_3$(OTf).[14] An unidentifiable mixture of products was obtained when the reaction was carried out using diethyl ketone.

The tentative mechanistic pathway for the formation of cyclobutanone derivative is described in Scheme 5. Reaction of 2 equiv of tertiary amine and 1 equiv of iodine would give the iminium iodide **I**.[12] Further reaction with

SCHEME 5. Tentative Mechanistic Pathway for the Formation of 3,3-Diarylcyclobutanone Derivatives



$TiCl_4$/*N,N*-diisopropyl-*N*-benzylamine could give the 1,3-dititanated iminium ion intermediate **IV** via the intermediacy of **III** (Scheme 5, path A). The reaction of the species **IV** with diaryl ketone could give the corresponding cyclobutanone derivative. However, the possibility of an alternative mechanism involving sequential metalation−addition reactions via the intermediates **III**, **V**, and **VI** cannot be ruled out (Scheme 5, path B).

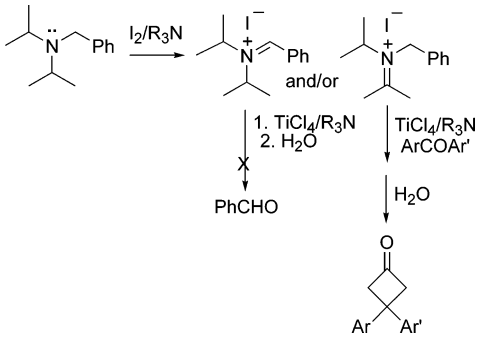
There are two possibilities for the iminium ion formation. It can form either at the isopropyl moiety or at the benzylic moiety. Since benzaldehyde was not isolated and the corresponding cyclobutanone was isolated as a major product in this reaction, the major pathway is the formation of iminium ion via deprotonation of the isopropyl group (Scheme 6).

Though the mechanistic path way involved is not clearly understood at this stage, the one-pot method of conversion of diaryl ketones to 3,3-diarylcyclobutanone derivatives described here may serve as a simple alternative procedure to hitherto known methods of synthesis of cyclobutanone derivatives.[4−9]

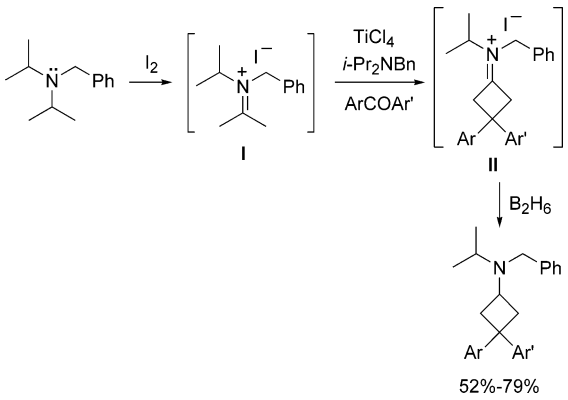
Synthesis of 3,3-Diarylcyclobutylamines by the Reduction of 3,3-Diarylcyclobutanone Iminium Ions by B_2H_6. It was reported that certain 3,3-diphenylcyclobutylamines are potential antidepressant agents.[2] These compounds strongly decrease the accumulation of noradrenaline (NA) and 5-hydroxytryptamine (5-HT) in brain slices in vitro and in vivo. It occurred to us that the reduction of the intermediate iminium ion (Scheme 7) in situ would lead to the corresponding cyclobutylamine derivatives. Indeed, we observed that when 3,3-

(13) Li, Z.; Sun, W.-H.; Jin, X.; Shao, C. *Synlett* **2001**, 1947.
(14) Iranpoor, N.; Zeynizaded, B. *Synlett* **1998**, 1079.

SCHEME 6. Two Possibilities of Formation of Iminium Ions from *N,N*-Diisopropyl-*N*-benzylamine and Iodine



SCHEME 7. One-Pot Synthesis of 3,3-Diarylcyclobutylamine Derivatives

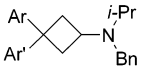
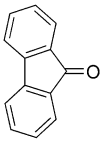
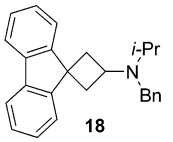
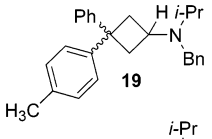
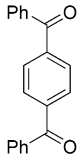
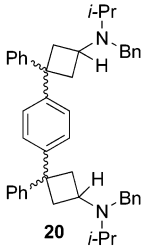


diarylcyclobutanone iminium salt prepared in situ is readily reduced with B_2H_6, generated using $NaBH_4/I_2$ reagent system,[15] to the corresponding 3,3-diarylcyclobutylamines in moderate to good yields (Scheme 7, Table 2). The reaction of symmetrical diaryl ketones produced the corresponding cyclobutylamines in moderate to good yields (entries 1−5). When an unsymmetrical diaryl ketone, 4-methylbenzophenone, was used, a mixture of isomers **19** was obtained in 69% yield. The reaction of 1,4-dibenzoylbenzene produced **20** as a mixture of isomers in 52% yield. Efforts to prepare iminium ions using the tertiary amines *N,N*-dimethyl-*N*-isopropylamine, *N*-isopropylpiperidine, and *N,N*-diisopropyl-*N*-methylamine and iodine were not successful. The formation of 3,3-diarylcyclobutylamine derivatives presented here also illustrates the intermediacy of 3,3-diarylcyclobutanone iminium ions in the reaction using $TiCl_4$/tertiary amines with diaryl ketones.

N,N-Dimethyl-3,3-diphenylcyclobutylamine is the most potent compound known to cause motor stimulation.[2] Therefore, it was of interest to synthesize such compounds by reductive amination of the readily accessible cyclobutanone derivatives. When 3,3-diarylcyclobutanone derivatives were treated with dimethylammonium formate,[2] the corresponding *N,N*-dimethylcyclobutylamine derivatives were obtained in 69−82% yields (Scheme 8). This method compares favorably with the multistep syntheses (∼10% overall yield) of such compounds following methods reported previously.[2]

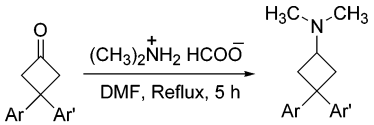
(15) Periasamy, M.; Narayana, C. *J. Organomet. Chem*. **1987**, *323*, 145.

TABLE 2. Reduction of 3,3-Diarylcyclobutanone Iminium Ions with B_2H_6

Entry	Substrate	Product[a]	Yield[b] %
			
1	Ar=Ar'=Ph	**14**	73
2	Ar=Ar'=4-ClC_6H_4	**15**	79
3	Ar=Ar'=4-FC_6H_4	**16**	76
4	Ar=Ar'=4-$OCH_3C_6H_4$	**17**	61
5		 **18**	54
6	Ar=Ph, Ar'=4-$CH_3C_6H_4$	 **19**	69
7		 **20**	52

[a] The products were identified by ^1H and ^{13}C NMR and mass spectral data. [b] The yields are based on the diaryl ketone used.

SCHEME 8. Synthesis of *N,N*-Dimethyl-3,3-diarylcyclobutylamines



Ar = Ar' = 4-ClC_6H_4, **21**, 75%

Ar = Ar' = 4-FC_6H_4, **22**, 82%

Ar = Ph, Ar' = 4-$CH_3C_6H_4$, **23**, 69%

Conclusions

A simple method of conversion of diaryl ketones to 3,3-diarylcyclobutanones using readily available starting materials has been developed. Convenient method of synthesis of 3,3-diarylcyclobutylamines, a system with promising biological activity, has been developed. A series of *N,N*-dimethyl-3,3-diarylcyclobutylamines have been synthesized by the reductive amination of the corresponding 3,3-diarylcyclobutanone derivatives. The availability of simple and efficient methods of synthesis of the cyclobutylamine system with potential biological activity should stimulate further research activities in this area.

Experimental section

Representative Procedure for the Preparation of 3,3-Diarylcyclobutanone Derivatives (5). Iodine (0.63 g, 2.5 mmol) and *N,N*-diisopropyl-*N*-benzylamine (0.96 g, 5 mmol) were taken in dichloroethane (40 mL) under N_2, and the mixture was refluxed at 95−100 °C for 2 h and brought to 25 °C under N_2. Benzophenone (0.46 g, 2.5 mmol) dissolved in 5 mL of dichloroethane was added, and $TiCl_4$ (1.65 mL of 1:1 solution of $TiCl_4$−CH_2Cl_2, 7.5 mmol) was added at 0 °C followed by *N,N*-diisopropyl-*N*-benzylamine (1.43 g, 7.5 mmol). The contents were stirred at 0 °C for 10 min and then refluxed at 95−100 °C for 6 h. The contents were brought to rt, and then a saturated NH_4Cl solution (20 mL) was added and the resulting mixture stirred for 0.5 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extract was washed with 5 N HCl (2 × 20 mL) to remove the unreacted amine, followed by water and brine solution (10 mL), and dried over anhydrous $MgSO_4$. The solvent was removed, and the residue was chromatographed on a silica gel column. Unidentified less polar compounds and the unreacted ketone were eluted using 1:99 EtOAc/hexane mixture. The 3,3-diphenylcyclobutanone **5** was eluted using 2:98 EtOAc/hexane (0.26 g, 76%). **5**: mp 83−84 °C (lit.[16] mp 84−85 °C); IR (cm^{-1}) $\nu_{C=O}$ 1786; ^{13}C NMR δ 205.2, 147.2, 128.7, 126.8, 126.5, 60.5, 42.0; ^1H NMR δ 7.40−7.20 (m, 10H), 3.80 (s, 4H). **6**: mp 110−112 °C; IR (cm^{-1}) $\nu_{C=O}$ 1790, 1770; ^{13}C NMR δ 203.7, 145.2, 132.7, 128.9, 128.0, 60.4, 41.3; ^1H NMR δ 7.32−7.20 (m, 8H), 3.77 (s, 4H); EI/MS *m/z* (r.i.) 294 [($M^+ - 1$) + 4, 1], 292 [($M^+ - 1$) + 2, 7], 290 [($M^+ - 1$), 11], 248 (100), 178 (94). **7**: mp 71−73 °C; IR (cm^{-1}) $\nu_{C=O}$ 1786; ^{13}C NMR δ 205.6, 144.6, 136.0, 129.3, 126.6, 60.5, 41.4, 20.9; ^1H NMR δ 7.30−7.18 (m, 8H), 3.80 (s, 4H), 2.40 (s, 6H); EI/MS *m/z* (r.i.) 250 (M^+, 36), 235 (72), 208 (100), 193 (99). **8**: mp 114−116 °C; IR (cm^{-1}) $\nu_{C=O}$ 1790, 1774; ^{13}C NMR δ 203.8, 163.9, 159.0, 142.8, 128.3, 115.8, 115.3, 60.7, 41.1; ^1H NMR δ 7.30−6.96 (m, 8H), 3.76 (s, 4H). Anal. Calcd for $C_{16}H_{12}F_2O$: C, 74.41; H, 4.68; F, 14.71; O, 6.20. Found: C, 74.51; H, 4.61. **9**: mp 64−65 °C; IR (cm^{-1}) $\nu_{C=O}$ 1790; ^{13}C NMR δ 205.2, 147.5, 144.3, 136.1, 129.4, 128.7, 126.7, 126.5, 60.5, 41.7, 20.9; ^1H NMR δ 7.40−7.20 (m, 9H), 3.85 (s, 4H), 2.40 (s, 3H); EI/MS *m/z* (r.i.) 236 (M^+, 38), 221 (40), 194 (94), 179 (100). **10**: mp 145−147 °C; IR (cm^{-1}) $\nu_{C=O}$ 1786; ^{13}C NMR δ 205.6, 150.0, 140.1, 128.0, 127.8, 121.8, 120.1, 58.9, 41.4; ^1H NMR δ 7.80−7.35 (m, 8H), 3.66 (s, 4H); EI/MS *m/z* (r.i.) 220 (M^+, 15), 178 (100). **11**: mp 153−155 °C; IR (cm^{-1}) $\nu_{C=O}$ 1784, 1768; ^{13}C NMR δ 207.4, 147.3, 128.3, 126.6, 126.4, 98.4, 68.7, 68.3, 66.6, 61.4, 37.0; ^1H NMR δ 7.4−7.2 (m, 5H), 4.2 (s, 9H), 4.0−3.7 (m, 4H); EI/MS *m/z* (r.i.) 330 (M^+, 54), 288 (100). **12**: mp 218−220 °C; IR (cm^{-1}) $\nu_{C=O}$ 1786, 1766; ^{13}C NMR δ 204.9, 146.9, 145.4, 128.7, 126.9, 126.7, 126.6, 60.4, 41.6; ^1H NMR δ 7.40−7.20 (m, 14H), 3.78 (s, 8H). Anal. Calcd for $C_{26}H_{22}O_2$: C, 85.22; H, 6.05; O, 8.73. Found: C, 85.31; H, 5.98.

Reaction of the Iminium Ion Intermediate with Acetophenone. Iodine (0.63 g, 2.5 mmol) and *N,N*-diisopropyl-*N*-benzylamine (0.96 g, 5 mmol) were taken in dichloroethane (40 mL) under N_2, and the mixture was refluxed at 95−100 °C for 2 h and brought to 25 °C under N_2. $TiCl_4$ (2.2 mL of 1:1 solution of $TiCl_4$−CH_2Cl_2, 10 mmol) was added at 0 °C followed by *N,N*-diisopropyl-*N*-benzylamine (1.91 g, 10 mmol). The contents were stirred at 0−25 °C for 1 h. Acetophenone (0.9 mL, 7.5 mmol) was then added at 25 °C and stirred further at 25 °C for 6 h. A saturated NH_4Cl solution (20 mL) was added and stirred for 0.5 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extract was washed with 5 N HCl (2 × 20 mL) to remove the unreacted amine, followed by water and brine solution (10 mL), and dried over anhydrous $MgSO_4$. The solvent was removed, and the residue was chromatographed on a silica gel column. Unidentified less polar compounds were first eluted using hexane, and then 1,3,5-triphenylbenzene **13** was eluted next (0.12 g, 16%). **13**: mp 172−174 °C (lit.[11] mp 172 °C); ^{13}C NMR δ 142.43, 141.25, 128.90, 127.59, 127.42, 125.53; ^1H NMR δ 7.80 (s, 3H), 7.75−7.30 (m, 15H); EI/MS *m/z* (r.i.) 306 (M^+, 100).

Representative Procedure for the Synthesis of 3,3-Diarylcyclobutylamine Derivatives. Iodine(0.63 g, 2.5 mmol) and *N,N*-diisopropyl-*N*-benzylamine (0.96 g, 5 mmol) were taken in dichloroethane (40 mL) under N_2, and the mixture was refluxed at 95−100 °C for 2 h and brought to 25 °C under N_2. Benzophenone (0.46 g, 2.5 mmol) dissolved in 5 mL of dichloroethane was added, and $TiCl_4$ (1.65 mL of 1:1 solution of $TiCl_4$−CH_2Cl_2, 7.5 mmol) was added at 0 °C followed by *N,N*-diisopropyl-*N*-benzylamine (1.43 g, 7.5 mmol). The contents were stirred at 0 °C for 10 min and then refluxed at 95−100 °C for 6 h. The contents were brought to rt, and the diborane, generated using a solution of iodine (2.52 g, 10 mmol) in diglyme (10 mL) and $NaBH_4$ (0.76 g, 20 mmol) in diglyme (10 mL), was bubbled through the solution at 0 °C for a period of 2 h. The outlet from the flask was vented through a mercury bubbler and a trap containing adequate amount of acetone to destroy excess diborane. When the bubbling of the gases in the reaction flask had ceased, the bubbler was removed under nitrogen and replaced by a glass stopper. The reaction was continued for a further period of 3 h at 25 °C. A saturated K_2CO_3 solution (20 mL) was added and stirred for 0.5 h. The reaction mixture was filtered through a Buchner funnel. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous K_2CO_3. The solvent was removed. The unreacted *N,N*-diisopropyl-*N*-benzylamine was distilled out under reduced pressure, bp 116−118 °C/34 mm (lit.[17] bp 118−120 °C/34 mm). The recovered *N,N*-diisopropyl-*N*-benzylamine can be used again for these reactions by redistilling it over CaH_2. The residue was chromatographed on a neutral alumina column. A small amount of unreacted *N,N*-diisopropyl-*N*-benzylamine was first eluted using 0.25:99.75 EtOAc−hexane mixture. The *N*-benzyl-*N*-isopropyl-3,3-diphenylcyclobutylamine was next eluted (0.65 g, 73%). **14**: mp 38−40 °C; ^{13}C NMR δ 151.2, 148.0, 142.4, 128.5, 128.3, 128.1, 126.9, 126.5, 125.9, 125.7, 125.4, 51.4, 50.7, 49.4, 45.2, 42.0, 18.9; ^1H NMR δ 7.64−7.16 (m, 15H), 3.70 (s, 2H), 3.64−3.44 (m, 1H) 3.24−2.96 (m, 3H), 2.80−2.60 (m, 2H), 1.12 (d, J = 6.84 Hz, 6H); EI/MS *m/z* (r.i.) 355 (M^+, 3), 264 (14), 175 (80), 91 (100). **15**: mp 94−96 °C; ^{13}C NMR δ 148.9, 145.9, 142.0, 131.7, 131.4, 128.6, 128.5, 128.2, 128.1, 127.1, 126.5, 51.1, 50.5, 49.3, 44.3, 41.8, 18.7; ^1H NMR δ 7.44−6.96 (m, 13H), 3.56 (s, 2H), 3.48−3.28 (m, 1H), 3.01 (quintet, J = 6.84 Hz, 1H), 2.88−2.72 (m, 2H), 2.56−2.40 (m, 2H), 1.00 (d, J = 6.84 Hz, 6H); EI/MS *m/z* (r.i.) 424 (M^+, 2), 298 (7), 174 (71), 91 (100). Anal. Calcd for $C_{26}H_{27}Cl_2N$: C, 73.58; H, 6.41; Cl, 16.71; N, 3.30. Found: C, 73.65; H, 6.39; N, 3.32. **16**: ^{13}C NMR δ 163.5, 163.3, 158.7, 158.5, 146.7, 143.4, 142.2, 128.4, 128.2, 128.0, 127.4, 127.2, 126.4, 115.4, 115.2, 115.0, 114.8, 51.1, 50.6, 49.3, 44.1, 42.1, 18.7; ^1H NMR δ 7.48−6.88 (m, 13H), 3.61 (s, 2H), 3.52−3.32 (m, 1H), 3.05 (quintet, J = 5.86 Hz, 6.84 Hz, 1H), 2.92−2.76 (m, 2H), 2.64−2.44 (m, 2H), 1.04 (d, J = 6.84 Hz, 6H); EI/MS *m/z* (r.i.) 391 (M^+, 1), 215 (6), 175 (95), 91 (100). **17**: ^{13}C NMR δ 157.6, 157.4, 143.9, 142.4, 140.4, 128.2, 128.0, 127.8, 126.8, 126.4, 113.8, 113.7, 55.2, 51.2, 50.6, 49.3, 43.8, 42.1, 18.9; ^1H NMR δ 7.50−6.78 (m, 13H), 3.83 (s, 3H), 3.79 (s, 3H), 3.63 (s, 2H), 3.54−3.36 (m, 1H), 3.06 (quintet, J = 5.86 Hz, 6.84 Hz, 1H), 2.94−2.80 (m, 2H), 2.64−2.44 (m, 2H), 1.06 (d, J = 6.84 Hz, 6H); GCMS, M^+ (*m/z*) 415. **18**: ^{13}C NMR δ 152.6, 151.3, 142.3, 139.7, 128.3, 128.1, 127.5, 127.1, 127.0, 126.6, 123.3, 122.6, 119.7, 119.4, 51.0, 50.6, 49.2, 46.4, 41.1, 18.9; ^1H NMR δ 7.90−7.24 (m, 13H), 4.26−4.06 (m, 1H), 3.84 (s, 2H), 3.20 (quintet, J = 5.86 Hz, 6.84 Hz, 1H), 2.86−2.68 (m, 2H), 2.62−2.46 (m, 2H), 1.20 (d, J = 6.84 Hz, 6H); EI/MS

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m/z (r.i.) 353 (M^+, 1%), 205 (6%), 174 (100%), 91 (100%). **19**: ^{13}C NMR δ 151.4, 148.4, 148.2, 145.0, 142.4, 135.1, 134.8, 129.2, 129.0, 128.3, 128.0, 126.8, 126.4, 125.8, 125.6, 125.3, 51.4, 50.7, 49.3, 44.7, 41.9, 20.9, 18.8; ^1H NMR δ 7.56−7.10 (m, 14H), 3.65 (s, 2H), 3.60−3.40 (m, 1H), 3.18−2.84 (m, 3H), 2.70−2.52 (m, 2H), 2.40 and 2.35 (2 peaks, mixture of two isomers), 1.08 (d, J = 6.84 Hz, 6H); EI/MS *m/z* (r.i.) 369 (M^+, 2), 278 (6), 175 (74), 91 (100). **20**: mp 132−134 °C; ^{13}C NMR δ 151.6, 148.3, 148.1, 145.1, 144.8, 142.4, 128.3, 128.1, 127.1, 127.0, 126.8, 126.5, 126.0, 125.8, 125.4, 51.4, 50.9, 50.7, 49.4, 44.9, 44.7, 42.2, 42.0, 19.0; ^1H NMR δ 7.60−7.10 (m, 24H), 3.70 (s, 4H), 3.62−3.40 (m, 2H), 3.24−2.88 (m, 6H), 2.76−2.52 (m, 4H), 1.16 (d, J = 6.84 Hz, 12H). Anal. Calcd for $C_{46}H_{52}N_2$: C, 87.29; H, 8.28; N, 4.43. Found: C, 87.25; H, 8.24; N, 4.48.

Synthesis of *N,N*-Dimethyl-3,3-diarylcyclobutylamine Derivatives. The reductive amination of 3,3-diarylcyclobutanone derivatives was carried out following a reported procedure.[2] A solution of the 3,3-diaryl cyclobutanone (2.5 mmol) in 5 mL of DMF was added to dimethylammonium formate [prepared from HCOOH (0.23 g, 5 mmol) and dimethylamine (0.8 g, 17.5 mmol) at −10 °C], and the mixture was heated under reflux for 5 h. Diethyl ether was added to the cooled reaction mixture, and the solution was extracted with 2 M HCl solution. The acidic extracts were made alkaline using a 50% NaOH solution and extracted with Et_2O. The ether extracts were combined and dried over $MgSO_4$. The solvent was evaporated, and the residue was chromatographed on an alumina column. The cyclobutylamine derivative was isolated by elution with 15% EtOAc−hexane mixture.

21: mp 110−112 °C; ^{13}C NMR δ 148.7, 145.9, 131.8, 131.5, 128.6, 128.5, 128.2, 127.3, 56.2, 43.0, 41.8, 40.5; ^1H NMR δ 7.36−7.04 (m, 8H), 3.00−2.84 (m, 2H), 2.74−2.42 (m, 3H), 2.14 (s, 6H); EI/MS *m/z* (r.i.) 71 (100). **22**: mp 82−84 °C; ^{13}C NMR δ 163.5, 163.3, 158.6, 158.5, 146.4, 143.4, 128.4, 128.2, 127.4, 127.2, 115.3, 115.2, 114.9, 114.8, 56.2, 42.8, 41.8, 40.8; ^1H NMR δ 7.40−6.82 (m, 8H), 3.00−2.82 (m, 2H), 2.74−2.44 (m, 3H), 2.14 (s, 6H); EI/MS *m/z* (r.i.) 287 (M^+, trace), 214 (7), 71 (100). **23**: ^{13}C NMR δ 151.0, 148.2, 147.9, 145.0, 135.2, 134.8, 129.1, 128.9, 128.3, 128.2, 126.9, 126.8, 125.9, 125.7, 125.4, 56.6, 43.5, 43.4, 41.9, 40.6, 20.9; ^1H NMR δ 7.52−7.04 (m, 9H), 3.10−2.94 (m, 2H), 2.80−2.50 (m, 3H), 2.20 (s, 6H); EI/MS *m/z* (r.i.) 265 (M^+, 1), 71 (100).

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Supporting Information Available: ^{13}C NMR spectra of compounds **4**−**12** and **14**−**23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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