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Lewis Acid-Catalyzed [4+2]Type Cycloadditions of Aldimines Bearing α-Hydrogens with 2-Silyloxy-1,3-butadienes

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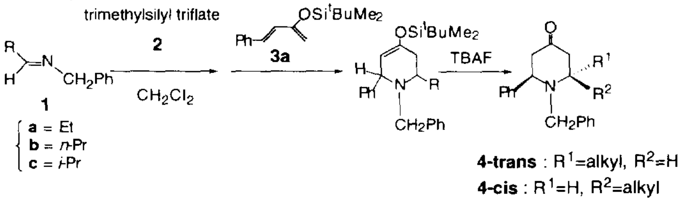
Abstract: *Trans*-2,6-disubstituted-4-piperidones were synthesized by [4+2]type cycloaddition of chiral aldimines (**5**) with 2-silyloxy-1,3-butadienes (**3**) in the presence of Lewis acids. In the cycloaddition, only two 2,6-*trans* isomers (chelation and non-chelation products) were observed and no *cis* compounds were detected regardless of the Lewis acid used. Chelation-controlled products **6b**, **8b**, and **9b** were obtained selectively by the use of $TiCl_4$-*i*-PrCN and **6a** was obtained with high selectivity when TMSOTf or $Zn(OTf)_2$ was used as a Lewis acid at 4 °C. The scope of the reaction is also described. © 1997 Elsevier Science Ltd.

INTRODUCTION

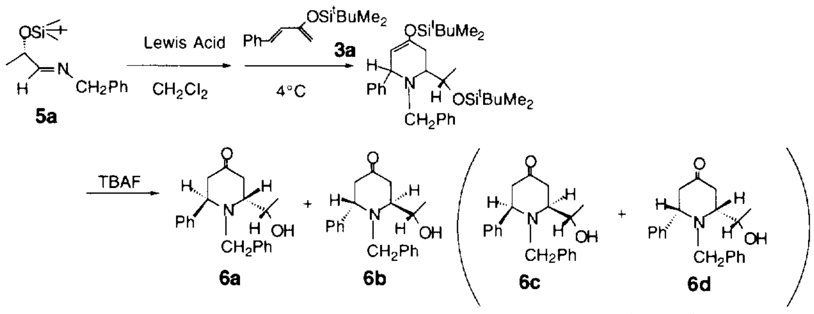
Nucleophilic addition reactions to aldimines have found widespread application in the synthesis of nitrogen-containing natural products.[1-3] However, the synthetic utility of reactions of aldimines bearing α-hydrogens with nucleophiles has been hampered by deprotonation of the α-hydrogens.[4] To overcome this problem, we and others have used soft nucleophiles such as copper reagents with Lewis acids.[5,6] In [4+2]type cycloaddition of aldimines, some workers have reported on reactions with activated aldimines,[1,7-13] highly nucleophilic Danishefsky's diene,[3,14-17] or catalytic activation by Lewis acids.[3,18,19] However, efficient [4+2]type cycloaddition of 2-silyloxy-1,3-butadienes with unactivated aldimines bearing α-hydrogens has not been reported. In our recent paper, we described the effective use of trimethylsilyl triflate for the cycloaddition.[20] The reaction of aldimines **1a**-**1c** with 2-silyloxy-1,3-butadiene **3a** in the presence of trimethylsilyl triflate gave good yields of cycloadducts **4** after deprotection with tetrabutylammonium fluoride (TBAF) (Scheme 1). It should be noted that the relative stereochemistry between C(2) and C(6) substituents in the major diastereomer of **4a** (R=Et) was assigned to be *trans* and higher *trans* selectivity was observed by increasing the bulkiness of the α-substituents of the aldimine (**4a** (R^1=Et), **4b** (R^1=*n*-Pr), and **4c** (R^1=*i*-Pr); the diastereomeric excess was 78 % (49 % isolated yield), 74 % (52 % isolated yield), and 96 % (75 % isolated yield), respectively). In this paper, we report on the stereoselective [4+2]type cycloaddition[21] of chiral aldimines **5a**-**5c**, which could easily be prepared from commercially available (*S*)-ethyl lactate or (*S*)-valine, to give 2,6-disubstituted-4-piperidones with exclusive *trans* geometry.



Scheme 1

RESULTS AND DISCUSSION

The α-silyloxyaldimines (**5a**, **5c**) and α-benzyloxyaldimine **5b** were easily prepared from commercially available (*S*)-ethyl lactate or (*S*)-valine.[22] [4+2]Type cycloaddition of aldimine **5a** with 2 equiv of 2-silyloxy-1,3-butadiene **3a** was conducted by the use of trimethylsilyl triflate in dichloromethane at 4 °C (Scheme 2). As expected from the effect of bulkiness of the α-substituent in **5**, only the two 2,6-*trans* diastereomers (**6a** and **6b**) were obtained as a 77:23 mixture in high yield (entry 1, Table 1). 2,6-*Cis* isomers were not detected at all. The stereochemistry of the major diastereomer **6a** was determined by X-ray analysis as an intramolecular hemiacetal (Figure 1) and the relative stereochemistry of minor diastereomer **6b** was confirmed to be *trans* between the α-hydroxyethyl group and the phenyl group by DIFNOE experiments. Proton irradiation of the C-6 methine group (-NC$\underline{H}$Ph-CH$_2$-: δ 3.80) of the ring resulted in intensity enhancement of signals of the methine proton (δ 4.48, 7.7 %) and the methyl protons (δ 1.20, 5.6 %) of the hydroxyethyl group, and no enhancement was observed of the signal of the C-2 methine group (δ 3.10). To achieve a higher degree of asymmetric induction from the α-chirality, we investigated the reaction with other Lewis acids under similar conditions (Table 1, entries 2-10). H_3SiOTf (entry 2) and *i*-Pr_3SiOTf (entry 3) did not show good selectivities in comparison with TMSOTf. Among a series of Lewis acids, it was interesting that the major product in the case of $Zn(OTf)_2$ (entry 4) was **6a** while the major one by using $TiCl_4$ was **6b** (entry 9). Therefore, we tried to optimize reaction conditions with these Lewis acids and an increase in the amount of **3a** to 4 equiv was found to be effective (entries 11 and 12).



not detected

Scheme 2

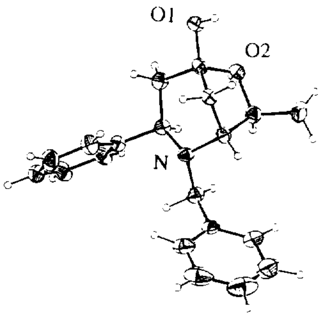


Figure 1. X-ray Crystallographic Structure of 6a.

Table 1. Effect of Lewis Acid on [4+2]Type Cycloaddition of an Aldimine (5a) with 2-Siloxy-1,3-butadiene (3a).

entry	Lewis acid	3a	6a:6b	yield(%)
1	TMSOTf	2eq to imine	77:23	90
2	H_3SiOTf	2eq to imine	55:45	91
3	TIPSOTf	2eq to imine	56:44	64
4	$Zn(OTf)_2$	2eq to imine	92:8	34
5	$BF_3 \cdot Et_2O$	2eq to imine	45:55	45
6	$ZnCl_2$	2eq to imine	37:63	78
7	$ZnBr_2$	2eq to imine	47:53	76
8	$SnCl_4$	2eq to imine	37:63	24
9	$TiCl_4$	2eq to imine	19:81	50
10	Ti(O*i*-Pr)4	2eq to imine	-	0
11	$Zn(OTf)_2$	4eq to imine	77:23	98
12	$TiCl_4$	4eq to imine	30:70	86

All reactions were carried out at 4 °C for 1-7 days in dichloromethane under nitrogen.

1.1 Equivalent of Lewis acid to **5a** was used in all reactions.

TMS: trimethylsilyl TIPS: triisopropylsilyl

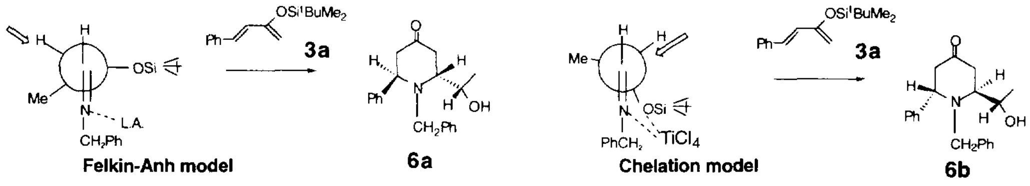


Figure 2

Formation of **6a** as in the case of $Zn(OTf)_2$ or TMSOTf can be explained by the non-chelation pathway and **6b** as with $TiCl_4$ by chelation model (Figure 2). The stereochemical outcome with $Zn(OTf)_2$ was a surprise for us but we reasoned that the formation of non-chelation product **6a** with $Zn(OTf)_2$ might be originated from the insolubility of $Zn(OTf)_2$ in dichloromethane. In the regular procedure, **3a** was added immediately after addition of **5a** within 5 sec to a suspension of $Zn(OTf)_2$ and **5a**. Thus, the complexation of $Zn(OTf)_2$ with **5a** was slow in the solvent and the non-chelation reaction with **3a** took place before chelation of the catalyst toward the silyloxy group occurred. In fact, the yield of the chelation product (**6b**) was increased (**6a**:**6b** = 62:38) when the mixture of $Zn(OTf)_2$ and **5a** was stirred for 30 min before addition of **3a**. Based on the results, we expected that even less polar solvents such as *n*-hexane would be more effective in the reaction with $Zn(OTf)_2$. The results of the solvent effect with $Zn(OTf)_2$ are shown in Table 2. To our delight, the diastereomer **6a** could be obtained with high selectivity (**6a**:**6b** = 89:11) in 93 % yield when $Zn(OTf)_2$ was used at 4 °C in dry *n*-hexane with 4 equiv of **3a** (entry 1). In contrast, the reaction with TMSOTf revealed no dependence on solvents although temperature effects were observed.

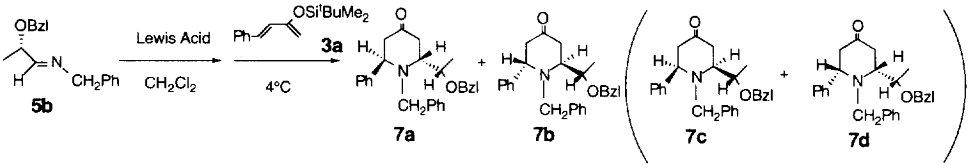
In the reaction with $TiCl_4$, we found that the following procedure gave the best results: To a stirred solution of **5a** was added $TiCl_4$ and **3a** successively. Since longer reaction time (20 min) of **5a** with $TiCl_4$ before addition of **3a** did not give **6** at all, it was necessary to add **3a** immediately after $TiCl_4$ was added to **5a**.

Table 2. Solvent Effect with TMSOTf or $Zn(OTf)_2$ as a Lewis Acid.

entry	solvent	Lewis acid	conditions	**6a**:**6b**	yield(%)
1	*n*-hexane	$Zn(OTf)_2$	4 °C, 2 days	89:11	93
2	*n*-hexane	$Zn(OTf)_2$	r.t., 1 day	94:6	53
3	toluene	TMSOTf	4 °C, 3 days	78:22	97
4	CH_2Cl_2	$Zn(OTf)_2$	4 °C, 4 days	77:23	98
5	CH_2Cl_2	TMSOTf	r.t., 3 days	66:34	76
6	CH_2Cl_2	TMSOTf	-78 °C, 7 days	51:49	39

1.1 Equivalent of Lewis acid to **5a** was used in all reactions.

Based on the chelation model, the use of a benzyl group instead of a TBDMS group for protection of a hydroxyl group was anticipated to yield **7b** with higher diastereoselectivity because chelation with $TiCl_4$ would become more facile (Scheme 3). The benzyl-protected aldimine **5b** was used in the reaction. The results are shown in Table 3. In spite of the use of 4 equiv of **3a**, yields were not good except for the case of TMSOTf (2 equiv of diene was used) and no product was obtained by using $TiCl_4$ (entries 1, 2, and 3, Table 3) because decomposition of **5b** had occurred. In addition, chelation-product **7b** was the minor product in all the cases. Therefore, it turns out that the bulky *t*-butyldimethylsilyl group is required for suppressing the decomposition of the aldimine effectively.



Scheme 3

Table 3. [4+2]Type Cycloaddition of α-Benzyloxyaldimine 5b.

entry	Lewis Acid	solvent	temperature (°C)	**7a** : **7b**	yield(%)
1	$TiCl_4$	CH_2Cl_2	4	-	0
2	$TiCl_4$	CH_2Cl_2	-20	-	0
3	$TiCl_4$	CH_2Cl_2	-78	-	0
4	$ZnCl_2$	CH_2Cl_2	4	84:16	25
5	$Zn(OTf)_2$	CH_2Cl_2	4	70:30	51
6	TMSOTf	CH_2Cl_2	4	78:22	95

1.1 Equivalent of Lewis acid to **5b** was used in all reactions.

All reactions were carried out at the shown temperature for 1 day.

A bulkier triisopropylsilyl-protected aldimine was used in the reaction with $TiCl_4$ at 4 °C in dichloromethane and the ratio was 40:60 (**6a**:**6b**) in 75% yield. The selectivity of **6b** formation was lower compared with the case of the *t*-butyldimethylsilyl-protected aldimine (**6a**:**6b** = 30:70, Table 1, entry 12). The inferior selectivity of **6b** formation might be attributed to the difficulty of chelation by the bulky triisopropylsilyl group. These results might suggest the presence of equilibrium between the *O*,*N*-chelated $TiCl_4$ complex and the *N*-coordinated complex, and thus, the selectivity observed with the *t*-butyldimethylsilyl-protected aldimine **5a** might be related with the equilibrium ratio of these species. In order to confirm the assumption, we examined temperature and solvent effects in the reaction with $TiCl_4$ (Table 4), under the speculation that the *O*,*N*-cyclic chelated $TiCl_4$ complex should be preferable to the *N*-acyclic complexed compound at low temperatures and in polar solvents. No product was obtained in acetonitrile but the result might be due to nucleophilic attack of **3a** at the acetonitrile cyano carbon. However, the use of bulkier isobutyronitrile and pivalonitrile as polar solvents was effective in affording **6b** selectively (entries 2 and 3). The best result was obtained (**6b** was obtained exclusively in 87% yield, entry 10) by using low melting isobutyronitrile (mp -72 °C) at -30 °C. The reversed selectivity observed in *n*-hexane (entry 9) may be ascribed to heterogeneous reaction conditions as was described in the reactions with $Zn(OTf)_2$.

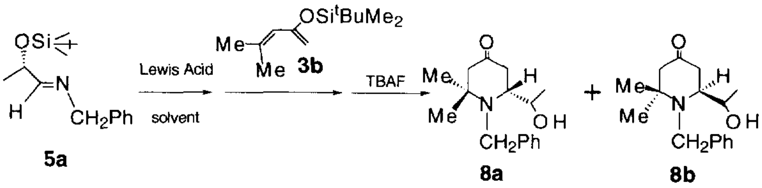
Table 4. Solvent and Temperature Effect on the Stereoselectivity of 6b Formation by Use of $TiCl_4$.

entry	solvent	conditions	**6a**:**6b**	yield(%)
1	CH_3CN	4 °C, 1 day	—	0
2	*i*-PrCN	4 °C, 1 day	24:76	67
3	*t*-BuCN	4 °C, 1 day	18:82	60
4	CH_2Cl_2 +sulfolane	4 °C, 1 day	24:76	65
5	CH_2Cl_2	4 °C, 1 day	30:70	86
6	Et_2O	4 °C, 1 day	53:47	96
7	CCl_4	4 °C, 1 day	49:51	71
8	toluene	4 °C, 1 day	68:32	90
9	*n*-hexane	4 °C, 1 day	>98:<2	12
10	*i*-PrCN	-30 °C, 1 day	<2:>98	87

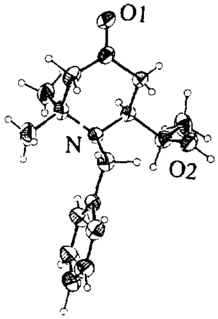
1.1 Equivalent of Lewis acid to **5a** was used in all reactions.

We also tried the reaction of **5a** with **3b** derived from mesityl oxide as shown in Scheme 4. The structural assignment for **8a** was carried out by X-ray crystal structure determination (Figure 3). The reactions using $Zn(OTf)_2$ and TMSOTf gave a mixture of **8a** and **8b** in the same ratio (43:57, Table 5, entries 2 and 3), and triisopropylsilyl-protected aldimine did not improve the ratio in the presence of TMSOTf at 4 °C in dichloromethane. As expected, **8b** could be obtained with high selectivity with $TiCl_4$ in *i*-PrCN (entry 1, Table 5).

The mechanism of [4+2]type cycloadditions involving aldimines is quite complex and a stepwise mechanism[23] and a concerted mechanism[19] have been suggested. Recently, we reported on [4+2]type cycloaddition of **3** to chromone[24] and coumarin[25] activated by TBDMSOTf (*t*-butyldimethylsilyl triflate) and it was concluded that only the former proceeded through a silyloxyallyl cation intermediate based on a successful trapping experiment by the use of sterically hindered **3b**. Therefore, in order to gain insight into the mechanism of the reaction of **5a** with **3b** catalyzed by TMSOTf, the mixture was quenched after stirring for 15 min at 0 °C. However, only cyclic products **8** were obtained in 63% yield and no acyclic products were isolated. In addition, only cyclic products **6** were isolated in 20% yield when the reaction of **5a** with **3a** was carried out at 0 °C for 1 min in the presence of TMSOTf. These results suggest that the reaction proceeds through a concerted mechanism or a stepwise mechanism in which cyclization of cation intermediates is fast.



Scheme 4



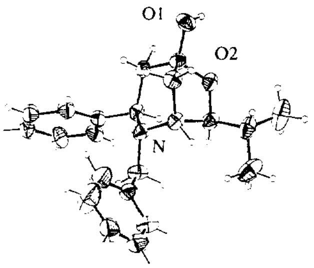


Figure 3. X-ray Crystallographic Structure of 8a.

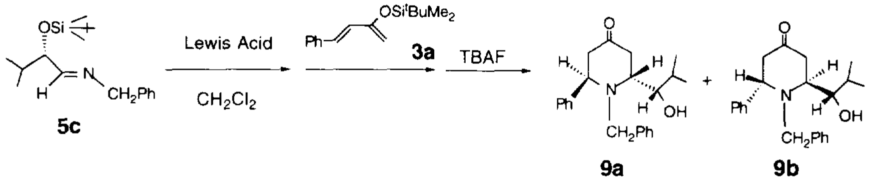
Figure 4. X-ray Crystallographic Structure of 9a.

Table 5. [4+2]Type Cycloaddition of 5a with 3b.

entry	solvent	Lewis acid	conditions	**8a**:**8b**	yield(%)
1	*i*-PrCN	$TiCl_4$	-30 °C, 1 day	9:91	65
2	*n*-hexane	$Zn(OTf)_2$	4 °C, 2 days	43:57	75
3	CH_2Cl_2	TMSOTf	4 °C, 1 day	43:57	80

1.1 Equivalent of Lewis acid to **5a** was used in all reactions.

When the aldimine **5c** bearing a bulkier isopropyl group at the α-position was subjected to cyclization with **3a** followed by subsequent treatment with TBAF, cycloadducts (**9a** and **9b**) could be obtained as expected (Table 6 and Scheme 5). The structural determination could be carried out similarly as mentioned above, and Figure 4 shows the X-ray structure of **9a**. In this case, non-chelation product **9a** could not be obtained selectively (entries 1 and 2). In addition, no product was observed in isobutyronitrile at -30 °C although **9b** could be obtained predominantly at 4 °C in dichloromethane (entry 3). Thus, the reaction was sluggish probably because of the steric hinderance of the *i*-Pr group in **5c**. Therefore, we tried to activate $TiCl_4$ by the use of silver ions. After some experiments, we found that addition of 1 equiv of AgOTf to the mixture was quite effective in activating $TiCl_4$ and only **9b** was obtained in 49 % yield at -30 °C in *i*-PrCN (entry 5).



Scheme 5

Table 6. [4+2]Type Cycloaddition of 5c with 3a.

entry	solvent	Lewis acid	conditions	**9a**:**9b**	yield(%)
1	CH_2Cl_2	TMSOTf	4 °C, 7 days	43:57	91
2	CH_2Cl_2	$Zn(OTf)_2$	4 °C, 7 days	49:51	59
3	CH_2Cl_2	$TiCl_4$	4 °C, 11 days	30:70	91
4	*i*-PrCN	$TiCl_4$	-30 °C, 1 day	-	0
5	*i*-PrCN	$TiCl_4$-AgOTf	-30 °C, 1 day	<2:>98	49

1.1 Equivalent of Lewis acid to **5c** was used in all reactions.

In conclusion, we have successfully carried out [4+2]type cycloaddition with unactivated aldimines derived from (*S*)-ethyl lactate or (*S*)-valine to yield *trans*-2,6-disubstituted-4-piperidones. The selectivities concerning the aldimine face could be controlled by the choice of Lewis acid and solvent.

EXPERIMENTAL

General.

^1H NMR spectra were recorded at 400 MHz (JEOL EX400) in $CDCl_3$. Chemical shifts (δ) are reported in ppm downfield from internal tetramethylsilane or from residual chloroform (δ=7.26). Melting points were measured with a Yanagimoto micromelting point apparatus and were uncorrected. High-resolution mass spectra were recorded on a JEOL SX-102A spectrometer. Elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer. Aldimines **5a**-**5c** were prepared by the reaction of the corresponding silyloxy- and benzyloxyaldehyde[26] with benzylamine in the presence of molecular sieves 4A in ether. The crude aldimines were purified by vacuum distillation.

Typical Procedures for $TiCl_4$-catalyzed [4+2]Type Cycloadditions:

Titanium tetrachloride (0.38 mmol) and 1.36 mmol of **3a** were added to 0.34 mmol of **5a** in dry isobutyronitrile (2.8 mL) at -30 °C under nitrogen. After stirring at -30 °C for 1 day, the reaction mixture was poured into aq $NaHCO_3$ followed by extraction with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated. The residue was dissolved in THF and 1.3 mmol of TBAF (in THF solution) was added to the solution. The reaction mixture was stirred for 10 h, quenched with water, extracted with CH_2Cl_2, and the combined organics were dried over $MgSO_4$. After the solvent was removed in vacuo, the crude product was separated by recycle HPLC (JAI LC 908, JAIGEL-1H and 2H, 1,2-dichloroethane).

Typical Procedures for Zn(OTf)$_2$-catalyzed [4+2]Type Cycloadditions:

To a stirred solution of 0.38 mmol of Zn(OTf)$_2$ in dry hexane (4.1 mL) was added 0.34 mmol of **5a** at 0 °C under nitrogen. Following the addition of **3a** (1.36 mmol), the mixture was stirred at 4 °C for 3 days. The resulting mixture was poured into aq $NaHCO_3$ and extracted with CH_2Cl_2. After the combined organic layers were dried over $MgSO_4$, the solvent was evaporated. The residue was dissolved in THF and 1.3 mmol of TBAF (in THF solution) was added to the solution. The reaction mixture was stirred for 10 h, quenched with water, extracted with CH_2Cl_2, and the combined organics were dried over $MgSO_4$. After the solvent was removed in vacuo, the crude product was separated by recycle HPLC (JAI LC 908, JAIGEL-1H and 2H, 1,2-dichloroethane).

Typical procedures for runs using TMSOTf were almost the same as for $TiCl_4$ except that dichloromethane or toluene was used as a solvent.

6a: colorless crystals (ether / *n*-hexane). mp 147-148 °C. ^{1}H NMR ($CDCl_3$): δ 1.20 (d, *J* = 6.4 Hz, 3H), 1.56 (brs, 1H), 1.81-2.08 (m, 4H), 3.10 (d, *J* = 4.4 Hz, 1H), 3.18 (d, *J* = 14.2 Hz, 1H), 3.63 (d, *J* = 14.2 Hz, 1H), 3.80 (dd, *J* = 5.4, 10.8 Hz, 1H), 4.48 (q, *J* = 6.4 Hz, 1H), 7.22-7.60 (m, 10H). Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.89; H, 7.66; N, 4.58.

6b: colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.04 (d, *J* = 5.8 Hz, 3H), 1.55 (brs, 1H), 2.30 (dd, *J* = 15.1, 3.9 Hz, 1H), 2.58-2.95 (m, 4H), 3.47 (d, *J* = 13.5 Hz, 1H), 3.78-3.90 (m, 2H), 4.52 (dd, *J* = 10.7, 3.9 Hz, 1H), 7.13-7.39 (m, 10H). HRMS: *m/z* Calcd for $C_{20}H_{23}NO_2$: 309.1729. Found: 309.1753.

7a: colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.31 (d, *J* = 6.4 Hz, 3H), 2.41 (dd, *J* = 14.9, 3.4 Hz, 1H), 2.66 (dd, *J* = 15.3, 6.3 Hz, 1H), 2.74-2.77 (m, 2H), 3.06-3.10 (m, 1H), 3.50-3.59 (m, 1H), 3.55 (d, *J* = 13.7Hz, 1H), 3.88 (d, *J* = 13.7Hz, 1H), 4.36 (d, *J* = 11.7 Hz, 1H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.90 (dq, *J* = 4.9, 6.4 Hz, 1H), 7.20-7.50 (m, 15H). HRMS: *m/z* Calcd for $C_{27}H_{29}NO_2$: 399.2199. Found: 399.2202.

7b: colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.17 (d, *J* = 6.4 Hz, 3H), 2.50-2.55 (m, 4H), 3.01-3.03 (m, 1H), 3.48 (d, *J* = 13.6 Hz, 1H), 3.63 (d, *J* = 13.6 Hz, 1H), 3.96-4.03 (m, 1H), 4.26-4.35 (m, 1H), 4.42 (d, *J* = 11.5Hz, 1H), 4.63 (d, *J* = 11.5 Hz, 1H), 7.05-7.45 (m, 15H). HRMS: *m/z* Calcd for $C_{27}H_{29}NO_2$: 399.2199. Found: 399.2188.

8a: colorless crystals (ether / *n*-hexane). mp 106-107 °C. ^{1}H NMR ($CDCl_3$): δ 0.94 (d, *J* = 6.8 Hz, 3H), 1.06 (s, 3H), 1.37 (s, 3H), 1.60 (brs, 1H), 2.20-2.31 (m, 2H), 2.65-2.83 (m, 3H), 3.35 (d, *J* = 17.1 Hz, 1H), 3.88-3.91 (m, 1H), 4.24 (d, *J* = 17.1 Hz, 1H), 7.22-7.47 (m, 5H). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.38; H, 8.84; N, 5.76.

8b: colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.96 (d, *J* = 6.3 Hz, 3H), 1.30 (s, 3H), 1.32 (s, 3H), 2.17-2.59 (m, 4H), 3.13 (dt, *J* = 8.6, 4.3 Hz, 1H), 3.52 (dq, *J* = 8.6, 6.3 Hz, 1H), 3.80 (d, *J* = 15.8 Hz, 1H), 4.00 (d, *J* = 15.8 Hz, 1H), 7.24-7.42 (m, 5H). HRMS: *m/z* Calcd for $C_{16}H_{23}NO_2$: 261.1729. Found: 261.1725.

9a: colorless crystals (ether / *n*-hexane). mp 158-159 °C. ^{1}H NMR ($CDCl_3$): δ 0.75 (d, *J* = 6.3 Hz, 3H), 1.05 (d, *J* = 6.3 Hz, 3H), 1.45-1.55 (m, 1H), 1.86-2.10 (m, 4H), 3.16 (d, *J* = 14.2 Hz, 1H), 3.15-3.25 (m, 1H), 3.60 (d, J = 14.2 Hz, 1H), 3.70-3.85 (m, 1H), 4.15-4.25 (m, 1H), 7.15-7.60 (m, 10H). Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 78.30; H, 8.27; N, 4.08.

9b: To an isobutyronitrile (2 mL) solution of **5a** (0.15 mL, 0.45 mmol) was added isobutyronitrile (4 mL) solution of titanium tetrachloride (0.08 ml, 0.68 mmol) and silver triflate (0.17 g, 0.69 mmol) at -30 °C under nitrogen. Following the addition of **3a** (0.45 mL, 1.8 mmol), the mixture was stirred at -30 °C for 1 day. The reaction mixture was poured into aq $NaHCO_3$ followed by extraction with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated. The residue was dissolved in THF and 1.8 mmol of TBAF (in THF solution) was added to the solution. The reaction mixture was stirred for 10 h, quenched with water, extracted with CH_2Cl_2, and the combined organics were dried over $MgSO_4$. After the solvent was removed in vacuo, the crude product was separated by recycle HPLC (JAI LC 908, JAIGEL-1H and 2H, 1,2-dichloroethane) to give **9b** (74 mg, yield 49 %) as colorless oil. ^1H NMR ($CDCl_3$): δ 0.60 (d, J = 6.3 Hz, 3H), 1.06 (d, J = 6.3 Hz, 3H), 1.70-1.85 (m, 1H), 2.36-2.45 (m, 1H), 2.70-2.85 (m, 2H), 2.98-3.10 (m, 1H), 3.20-3.25 (m, 1H), 3.62 (d, J = 14.0 Hz, 1H), 3.58-3.63 (m, 1H), 3.90 (d, J = 14.0 Hz, 1H), 4.63-4.70 (m, 1H), 7.20-7.75 (m, 10H). HRMS: m/z Calcd for $C_{22}H_{27}NO_2$: 337.2042. Found: 337.2032.

Crystal Structure of 6a, 8a, and 9a.

Crystallographic data for **6a:** $C_{20}H_{23}NO_2$, FW = 309.0, *orthorhombic*, space group $P2_12_12_1$, a = 11.380(2) Å, b = 25.362(2) Å, c = 6.016(2) Å, V = 1736.4(7) Å^3, Z = 4, D cal = 1.18 g/cm^3, μ = 0.42 cm^{-1}. T = 297 K. Final R = 0.054 (Rw= 0.063) for 1389 observed reflections with $F>3\sigma(F)$. Crystallographic data for **8a:** $C_{16}H_{23}NO_2$, FW = 261.4, *monoclinic*, space group $P2_1/n$, a = 15.878(4) Å, b = 7.721(2) Å, c = 13.083(4) Å, β = 111.53(2) °, V = 1492.1(7) Å^3, Z = 4, D cal = 1.16 g/cm^3, μ = 0.42 cm^{-1}. T = 297 K. Final R = 0.071 (Rw= 0.094) for 1645 observed reflections with $F>3\sigma(F)$. Crystallographic data for **9a:** $C_{22}H_{27}NO_2$, FW = 337.0, *Trigonal*, space group $P322_1$, a = 10.478(2) Å, b = 10.478(2) Å, c = 31.20(1) Å, V = 2966(2) Å^3, Z = 6, D cal = 1.13 g/cm^3, μ = 0.39 cm^{-1}. T = 297 K. Final R = 0.076 (Rw= 0.066) for 1242 observed reflections with $F>3\sigma(F)$.

Crystals suitable for X-ray structure determination were mounted on a Mac Science MXC3 diffractometer and irradiated with graphite-monochromated Mo $K\alpha$ radiation (λ = 0.71073 Å) for data collection. Lattice parameters were determined by least-squares fitting of 21-31 reflections with $27°<2\theta<32°$, $19°<2\theta<30°$, and $24°<2\theta<35°$ for **6a**, **8a**, and **9a**, respectively. Data were collected with the $2\theta/\omega$ scan mode. The structure was solved by a direct method with a program, Monte Carlo-Multan.[27] Refinement on F was carried out by full-matrix least-squares. All non-hydrogen atoms were refined with anisotropic themal parameters. All hydrogen atoms in **6a** and **8a** could be found on a difference Fourier map; these coordinates were included in the refinement with isotropic thermal parameters. The hydrogen atoms in **9a** were included in the refinement on calculated positions (C-H = 1.0 Å) riding on their carrier atoms with isotropic thermal parameters. All the computations were carried out on a Titan-750 computer using the crystan-G program. Atomic coordinates, bond distances and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Center.

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