Preparation of β-Lactams by Mannich-Type Addition of Ethyl(trimethylsilyl)acetate (ETSA) to *N*-(2-Hydroxyphenyl)aldimine Sodium Salts

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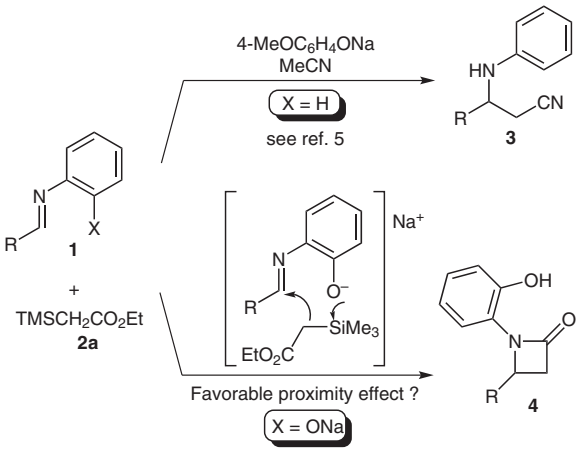
Abstract: The synthesis of highly substituted β-lactams was achieved by addition of air-stable ethyl(trimethylsilyl)acetate derivatives to *N*-(2-hydroxyphenyl)aldimine sodium salts in a THF–EtCN mixture. This reaction proceeds with moderate to good yields and diastereomeric ratio of up to 78:22. The reactivity of the *N*-(2-hydroxyphenyl)aldimine can be modified by simply changing the co-solvent from EtCN to MeCN to afford the cyanomethylated addition product.

Key words: imines, lactams, silicon, phenols, tandem reactions

β-Lactams (azetidin-2-ones) are important compounds in organic chemistry due to their biological activity[1] and their easy transformation into more complex molecules.[2] Accordingly, much attention and effort have been devoted in the past to the preparation of β-lactams. Among all the existing methods[3] [i.e. reaction of imines with ketenes, [2+2]-cycloaddition of isocyanates to alkenes, reaction of nitrones with terminal alkynes catalyzed by Cu(I), cyclization reactions], the enolate–imine condensation is one the most attractive because of its easiness to implement and its efficiency, affording products in good yields under rather mild conditions. In the last past years, various catalytic Mannich-type additions of silyl enolates to aldimines have been successfully reported.[4] However, the poor stability of these silyl enolates along with their limited accessibility may limit seriously such strategies in synthetic applications. Herein, we report our investigation on the use of more stable and readily accessible ethyl(trimethylsilyl)acetate (ETSA) derivatives in Mannich-type additions to provide an easy access to β-lactams.

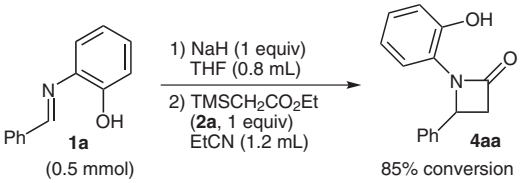
We recently reported the direct addition of alkyl nitriles to unactivated imines using a catalytic ETSA–phenoxide sodium salt combination as source of ethyl acetate enolate.[5] Under these conditions, the alkyl nitrile is initially deprotonated by ethyl acetate enolate prior to reaction with the aldimine. The resulting catalytic amide salt intermediate, basic enough to deprotonate the alkyl nitrile, is then involved in an autocatalytic process (Scheme 1). According to this mechanism, we postulated that *N*-(2-hydroxyphenyl)aldimine sodium salts might display a favorable proximity effect[6] between the putative activated ETSA (**2a**) and the imine double bond to promote the formation of β-lactams **4** via the cyclization of ETSA addition products intermediately formed (Scheme 1).



Scheme 1 Mannich-type addition of ETSA to *N*-(2-hydroxyphenyl)aldimine sodium salts: working hypothesis

In a first attempt, the sodium salt of *N*-(2-hydroxyphenyl)benzaldimine (**1a**) was generated by addition of a solution of **1a** in THF to a solution of NaH in THF followed by addition of ETSA (**2a**; 1 equiv) and a large excess of acetonitrile (MeCN).[7] Under these conditions, the presence of the phenoxide sodium salt within the aldimine substrate **1a** did not change the outcome of the reaction, affording MeCN addition product **3a** in 57% yield as previously observed under autocatalytic conditions.[5]

Surprisingly, switching the solvent system from THF–MeCN to THF–EtCN had a dramatic effect on the course of the reaction. Thus, by conducting the reaction at room temperature for two hours, we were pleased to observe formation of the β-lactam **4aa** in 85% conversion as the sole product of the reaction. A complete conversion could be reached by using ETSA in slight excess (Scheme 2).



Scheme 2 Effect of the solvent on the course of Mannich-type addition of ETSA

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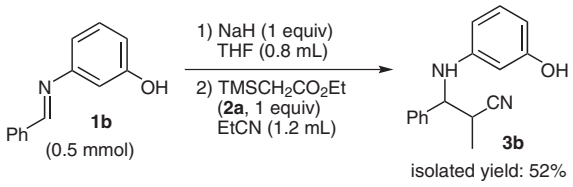
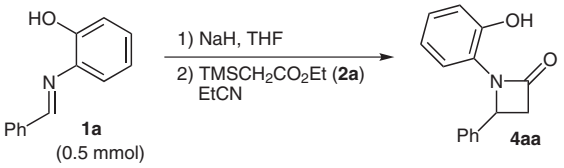
It is worth noting that conducting the reaction with *N*-(3-hydroxyphenyl)benzaldimine (**1b**), no β-lactam could be detected. The only product of the reaction was the propionitrile addition product **3b** obtained as a 1:1 mixture of diastereomers in 52% isolated yield.[8] These findings point out the importance of the position of the Lewis base (i.e. sodium phenoxide) to set properly the activated ETSA with respect to imine function, while strongly arguing in favor of an intramolecular activation process (Scheme 3).



Scheme 3 Effect of the substrate on the course of the Mannich-type reaction

Then, different reaction conditions were screened to ensure a complete conversion of **1a** to **4aa** (Table 1).

Table 1 Optimization of the Reaction Conditions



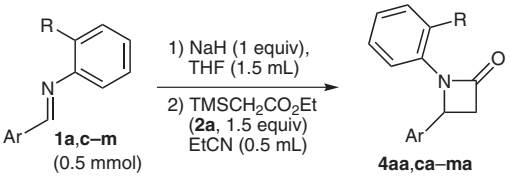
Entry	NaH (equiv)	ETSA (equiv)	Solvent A (mL)	Solvent B (mL)	Conversion (%)[a]
1	1	1.0	EtCN (1.2)	THF (0.8)	85
2	1	1.5	EtCN (1.2)	THF (0.8)	100
3	1	1.5	EtCN (0.5)	THF (1.5)	100
4	1	1.5	EtCN (0.1)	THF (1.9)	87
5	1	1.5	DMF (0.5)	THF (1.5)	55
6	1	1.5	THF (2)	–	0
7	0.2	1.5	EtCN (0.5)	THF (1.5)	0

[a] Determined by ^{1}H NMR after 2 h of reaction.

We first tried to optimize the quantity of ETSA (**2a**) and we found that the use of 1.5 equivalents furnished a complete conversion (Table 1, entries 1 and 2). A brief survey of solvents revealed that THF failed to promote the reaction in the absence of propionitrile, while addition of DMF as co-solvent provided β-lactam **4aa** in 55% conversion (Table 1, entry 5). These findings highlight the need to carry out the reaction in a solvent able to promote the activation of ETSA through coordination to silicon.

Next, we investigated the scope and limitation of β-lactam formation under the best conditions selected (i.e. THF–EtCN;[9] Table 2).

Table 2 ETSA Addition to Various Unactivated Imines



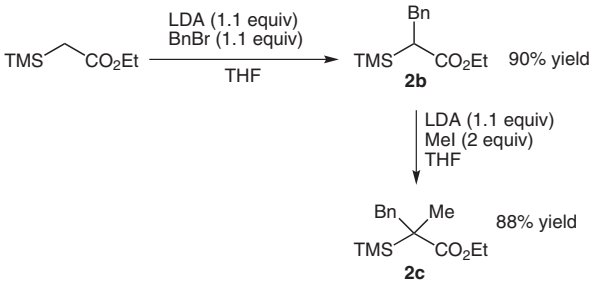
Entry	1	Ar	R	4: yield (%)[a]
1	**1a**	Ph	OH	**4aa**: 69
2	**1c**	2-naphthyl	OH	**4ca**: 63[b]
3	**1d**	3,4-$OCH_2OC_6H_3$	OH	**4da**: 58[b]
4	**1e**	4-$MeOC_6H_4$	OH	**4ea**: 62[b]
5	**1f**	4-$(Me)_2NC_6H_4$	OH	**4fa**: 25[c]
6	**1g**	4-PhC_6H_4	OH	**4ga**: 60[b]
7	**1h**	4-EtC_6H_4	OH	**4ha**: 58
8	**1i**	4-ClC_6H_4	OH	**4ia**: 68[b]
9	**1j**	4-CNC_6H_4	OH	**4ja**: 40
10	**1k**	4-$CF_3C_6H_4$	OH	**4ka**: 59
11	**1l**	2-FC_6H_4	OH	**4la**: 51[b]
12	**1m**	2-HOC_6H_4	H	**4ma**: 0

[a] Isolated yield; complete conversions were observed unless otherwise indicated.
[b] The use of 1:1 ratio of THF–EtCN was necessary to ensure complete conversion.
[c] The use of 0.6:1.4 ratio of THF–EtCN was necessary to ensure maximum (42%) conversion.

The various substituted *N*-(2-hydroxyphenyl)aldimines **1a** and **1c–l** afforded the β-lactams **4aa**, **4ca–la** in modest to good yields (Table 2, entries 1–11). Although in all cases NMR analysis revealed that the reaction proceeded to completion, aldimines **1f** and **1j** (Table 2, entries 5 and 9) provided rather modest isolated yields mainly due to difficulties encountered in the purification step. Aniline imine of 2-hydroxybenzaldehyde **1m** treated with one equivalent of sodium hydride failed to promote the reaction providing further evidence for the importance of the 2-hydroxyl group on aniline moiety (Table 2, entry 12).

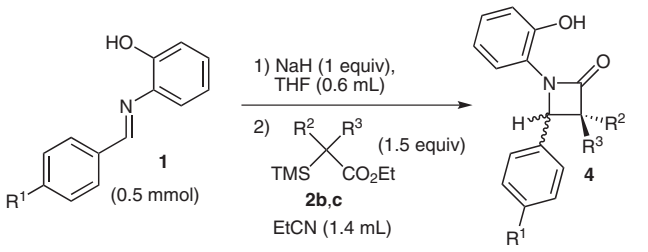
We next envisaged using various substituted ETSA derivatives to have access to highly substituted β-lactams. Compounds **2b–c** were easily prepared by deprotonation–alkylation sequences in good overall yields[10] (Scheme 4) and were reacted with an assortment of aldimines **1a–k** (Table 3).

Isolated yields ranged from 38% to 70%, while as previously noticed, the reaction was completed within two hours in almost all cases. When ETSA derivative **2c** reacted with aldimines **1a**, **1i** and **1k** (Table 3, entries 2, 4 and 5) some diastereoselectivity could be obtained in favor of the *trans* isomer,[11] while no diastereoselection was re-



Scheme 4 ETSA functionalization

Table 3 Substituted ETSA Addition to Unactivated Imines

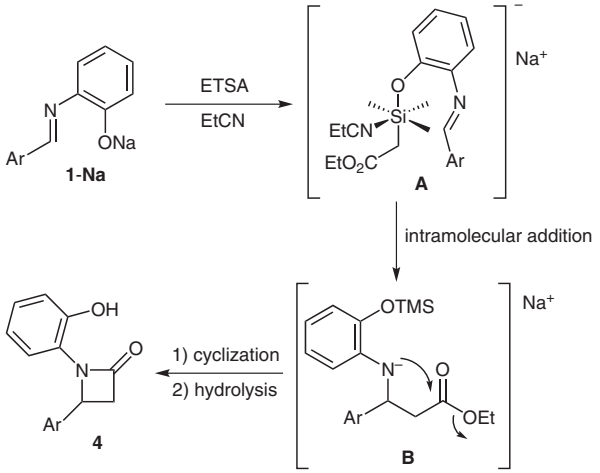


Entry	**1**	R^1	**2**	R^2	R^3	**4**: Yield (%)[a]	*cis*/*trans*[b]
1	**1a**	H	**2b**	Bn	H	**4ab**: 58	54:46
2	**1a**	H	**2c**	Bn	Me	**4ac**: 56	30:70
3	**1e**	OMe	**2c**	Bn	Me	**4ec**: 38[c]	46:54
4	**1i**	Cl	**2c**	Bn	Me	**4ic**: 70	22:78
5	**1k**	CF_3	**2c**	Bn	Me	**4kc**: 43	24:76

[a] Isolated yield; complete conversions were observed unless otherwise indicated.
[b] Ratio determined by ^{1}H NMR of the crude product.
[c] Conversion: 80%.

corded in the other experiments (Table 3, entries 1[12] and 3).

Although not clearly elucidated, a plausible mechanism is proposed in Scheme 5.



Scheme 5 Proposed mechanism for the formation of β-lactams

The first step would involve the coordination of the silicon atom of ETSA to the Lewis base **1-Na** to form a hypervalent silicon species **A**.[13] A rapid screening of the solvents gave some evidences that an additional coordination to silicon is crucial and suggests the formation of a hexavalent silicon complex as the most likely reactive species. The second step would take advantage of a favorable proximity effect to promote an intramolecular addition of the activated ETSA to the double bond imine; the resulting sodium amide salt **B** affording the desired β-lactams **4** after subsequent cyclization and hydrolysis of the silyloxy group.

In conclusion, we have reported a straightforward approach for the preparation of β-lactams in moderate to good yields by making use of stable ETSA or substituted derivatives and *N*-(2-hydroxyphenyl)aldimines **1**. The importance of the solvent system in the outcome of the reaction was evidenced by changing the co-solvent of the reaction from MeCN to EtCN. Whereas the use of MeCN lead to MeCN addition products,[5] β-lactams **4** were exclusively formed in the presence of propionitrile. On the basis of experimental data, an intramolecular activation of ETSA by the sodium phenoxide salt has been suggested as a key mechanistic element in the formation of ETSA addition products. Furthermore, *N*-(2-hydroxyphenyl)aldimines **1** may offer the advantage of easy removal of the *N*-aryl group in β-lactams **4** by an *O*-methylation–CAN [or $PhI(OAc)_2$] deprotection sequence[6b,d] or by a direct CAN deprotection.[14]

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(5) Poisson, T.; Gembus, V.; Oudeyer, S.; Marsais, F.; Levacher, V. *J. Org. Chem.* **2009**, *74*, 3516.
(6) For examples of the beneficial effect of the 2-aminophenol-derived imines in nucleophilic addition reactions, see: (a) Kobayashi, S.; Komiyama, S.; Ishitani, H. *Angew. Chem. Int. Ed.* **1998**, *37*, 979. (b) Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762. (c) Xue, S.; Yu, S.; Deng, Y.; Wulff, W. D. *Angew. Chem. Int. Ed.* **2001**, *40*, 2271. (d) Sugiura, M.; Robvieux, F.; Kobayashi, S. *Synlett* **2003**, 1749. (e) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566. (f) Rabbat, P. M. A.; Corey Valdez, S.; Leighton, J. L. *Org. Lett.* **2006**, *8*, 6119. (g) Jagtap, S. B.; Tsogoeva, S. B. *Chem. Commun.* **2006**, 4747.
(7) **Typical Procedure for the Preparation of 3a**: To a suspension of NaH (0.5 mmol, 0.013 g) in THF (0.4 mL) was added imine (0.5 mmol) as a solution in THF (0.4 mL). Then MeCN (1.2 mL) was added. After 5 min, $TMSCH_2CO_2Et$

(0.092 mL, 0.5 mmol) was added and the resulting mixture was stirred until complete disappearance of the starting materials. The solution was poured into brine and extracted with Et_2O (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography to afford the corresponding cyanomethylated product.

3-Phenyl-3-(2-hydroxyphenylamino)propanenitrile (3a): orange solid; mp 119–120 °C. Purification: SiO_2; 30% Et_2O in PE. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.86 (d, *J* = 6.2 Hz, 2 H), 4.72 (t, *J* = 6.4 Hz, 1 H), 6.52 (d, *J* = 7.9 Hz, 1 H), 6.62–6.68 (m, 1 H), 6.73–6.78 (m, 2 H), 7.31–7.43 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.4, 54.9, 113.8, 114.8, 117.5, 119.3, 121.4, 126.3, 128.5, 129.2, 134.5, 140.0, 144.3. FTIR (KBr): 610, 703, 734, 1128, 1199, 1244, 1445, 1510, 1522, 1613, 2264, 3380 cm^{-1}. HRMS (EI): *m*/*z* calcd for $C_{15}H_{14}N_2O$: 238.1106; found: 238.1111.

(8) **Spectral Data for 2-Methyl-3-phenyl-3-(3-hydroxyphenylamino)propanenitrile (3b)**: pale yellow solid; mp <50 °C (*syn*/*anti* = 1:1 mixture). Purification: SiO_2; 30–50% Et_2O in PE. ^1H NMR (300 MHz, $CDCl_3$; *syn*/*anti* = 1:1 mixture): δ = 1.12 (d, *J* = 7.2 Hz, 3 H), 1.27 (d, *J* = 7.2 Hz, 3 H), 2.29–2.95 (m, 1 H), 3.11–3.17 (m, 1 H), 4.32–4.37 (m, 1 H + 1 H), 5.98–6.00 (m, 2 H), 6.07–6.12 (m, 4 H), 6.83–6.90 (m, 2 H), 7.16–7.23 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$; *syn*/*anti* = 1:1 mixture): δ = 14.9, 16.0, 59.4, 59.9, 101.1, 105.8, 105.9, 106.8, 120.9, 126.0, 126.6, 127.3, 128.4, 128.6, 129.0, 130.3, 130.4, 130.5, 137.9, 139.6, 147.6, 147.9, 156.8, 156.9. FTIR (KBr): 772, 1161, 1219, 1338, 1599, 1732, 2921, 3378 cm^{-1}. HRMS (EI): *m*/*z* calcd for $C_{16}H_{16}N_2O$: 252.1263; found: 252.1272.

(9) **Typical Procedure for the Preparation of 4**: To a suspension of NaH (0.5 mmol, 0.013 g) in THF (0.5 mL) was added imine (0.5 mmol) as a solution in THF (1 mL). Then EtCN (0.5 mL) was added. After 5 min, $TMSCH_2CO_2Et$ (0.138 mL, 0.75 mmol) was added and the resulting mixture was stirred until complete disappearance of the starting materials. The solution was poured into brine and extracted with Et_2O (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography to afford the corresponding β-lactam.

1-(2-Hydroxyphenyl)-4-(2-naphthyl)azetidin-2-one (4ca): pale yellow solid; mp 136–138 °C. Purification: SiO_2; 20–30% Et_2O in PE; R_f 0.56 (33% EtOAc in PE). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.99 (dd, *J* = 15.6, 2.4 Hz, 1 H), 3.58 (dd, *J* = 15.4, 5.4 Hz, 1 H), 5.22 (dd, *J* = 2.3, 1.8 Hz, 1 H), 6.54–6.62 (m, 2 H), 6.99–7.04 (m, 2 H), 7.43–7.55 (m, 3 H), 7.83–7.89 (m, 4 H), 9.92 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 43.9, 54.3, 117.6, 119.0, 119.8, 122.7, 125.6, 125.9, 126.7, 126.9, 127.9, 128.0, 129.6, 133.3, 133.5, 134.4, 147.7, 166.2. FTIR (KBr): 742, 1377, 1495, 1707, 2967, 3016 cm^{-1}. HRMS (EI): *m*/*z* calcd for $C_{19}H_{15}NO_2$: 289.1103; found: 289.1106.

3-Benzyl-1-(2-hydroxyphenyl)-3-methyl-4-[4-(trifluoromethyl)phenyl]azetidin-2-one (4kc): purification: SiO_2; 10–15% Et_2O in PE.

trans Isomer: white solid; mp 154–156 °C; R_f 0.47 (30% Et_2O in PE). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.93 (s, 3 H), 3.09 (d, *J* = 14.0 Hz, 1 H), 3.26 (d, *J* = 13.9 Hz, 1 H), 5.17 (s, 1 H), 6.32 (dd, *J* = 0.8, 7.7 Hz, 1 H), 6.61–6.67 (m, 1 H), 7.04–7.07 (m, 4 H), 7.30–7.42 (m, 5 H), 7.54 (d, *J* = 8.8 Hz, 2 H), 9.79 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.8, 41.8, 57.0, 62.2, 117.9, 119.3, 119.9, 124.8, 125.7, 125.8, 125.9, 125.95, 126.0, 127.0, 127.1, 127.6, 128.9, 130.2, 130.3, 130.7, 135.8, 138.5, 147.8, 171.9.

cis Isomer (*trans*/*cis* mixture = 63:36): pale yellow oil; R_f 0.28 (30% Et_2O in PE). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.50 (s, 3 H), 2.26 (d, *J* = 14.1 Hz, 1 H), 2.74 (d, *J* = 14.1 Hz, 1 H), 5.04 (s, 1 H), 6.43 (app. d, *J* = 7.6 Hz, 1 H), 6.60–6.67 (m, 1 H), 6.90–6.94 (m, 2 H), 7.03–7.08 (m, 3 H), 7.09–7.13 (m, 3 H), 7.30–7.41 (m, 1 H), 7.57 (app. d, *J* = 8.1 Hz, 2 H), 9.85 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0, 38.6, 56.1, 66.3, 118.1, 119.6, 120.1, 125.2, 126.15, 126.2, 126.25, 126.3, 127.0, 127.2, 127.8, 129.2, 130.2, 130.4, 135.6, 138.4, 148.1, 172.0. FTIR (KBr): 748, 1068, 1125, 1168, 1326, 1498, 1714, 2929, 3067 cm^{-1}. HRMS (EI): *m*/*z* calcd for $C_{24}H_{20}NO_2F_3$: 411.1446; found: 411.1450.

(10) **Typical Procedure for the Preparation of 2b and 2c**: To a solution of diisopropylamine (1.1 equiv) in anhyd THF was added *n*-BuLi (2.5 M in hexane, 1.1 equiv) dropwise at –78 °C under nitrogen. The solution was warmed to r.t. for 10 min, then cooled to –78 °C prior to addition of ETSA (1 equiv) dropwise over 5 min. The solution was maintained at –78 °C for further 1 h before addition of the electrophile (1.1 equiv for BnBr or 2 equiv for MeI). The resulting solution was warmed to r.t. and stirred until complete disappearance of the starting materials. Saturated aq NH_4Cl solution was added and the mixture was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine and then dried over anhyd $MgSO_4$. The residue was purified by flash chromatography to afford the alkylated product. Spectral data of **2b** were in agreement with those described in the literature: Kuwajima, I.; Matsumoto, K.; Inoue , T. *Chem. Lett.* **1979**, *8*, 41.

Ethyl 2-Methyl-3-phenyl-2-(trimethylsilyl)propanoate (2c): colorless oil. Purification: SiO_2; 0–2% EtOAc in PE; R_f 0.73 (10% EtOAc in PE). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.00 (s, 9 H), 0.91 (s, 3 H), 1.09 (t, *J* = 7.2 Hz, 3 H), 2.33 (d, *J* = 13.4 Hz, 1 H), 3.40 (d, *J* = 13.4 Hz, 1 H), 3.96 (q, *J* = 7.0 Hz, 2 H), 6.97–7.10 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.1, 14.2, 15.9, 20.6, 37.9, 38.9, 59.6, 125.9, 127.8, 129.5, 176.0. FTIR (KBr): 844, 1180, 1199, 1252, 1262, 1454, 1715, 2963, 3030 cm^{-1}. HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{24}O_2Si$: 265.1624; found: 265.1631..

(11) A NOESY experiment was conducted on *trans*-**4kc**. Strong NOE correlation was observed between CH_2Ph and H(4) indicating a *cis* relationship between these substituents. The stereochemistry of the other β-lactams **4** was assigned by extrapolation of these findings along with the fact that H(4) of the major isomer always exhibit a higher chemical shift than that observed in the minor isomer.

(12) *cis*- and *trans*-β-Lactam **4ab** resulting from the reaction with **2b** can be easily identified by comparison with literature data: Jiao, L.; Liang, Y.; Xu, J. *J. Am. Chem. Soc.* **2006**, *128*, 6060.

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