Organic & Biomolecular Chemistry

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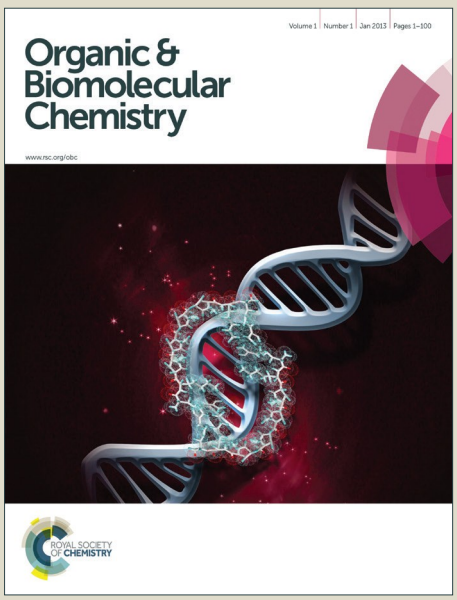

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PAPER

Catalytic cycloaddition of 2-hydroxy ketones with 1,1-dicyanoalkenes

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A tin-catalyzed reaction of α-hydroxy ketones with 1,1-dicyanoalkenes produced 2-amino-4,5-dihydrofuran-3-nitriles. In the catalytic reaction, tin enolates were generated from α-hydroxy ketones as active catalytic species. The highly basic ability of the Sn-O bonds played an important role in the reactions. This tin-catalyzed reaction was highly atom-economical and required no other metal reagents.

Introduction

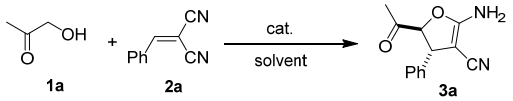
Organotin enolates act as efficient carbon nucleophiles to generate carbon-carbon bonds, and are more reactive than silyl enolates but less basic than the lithium versions.[1] Tin enolates are difficult to handle compared with silyl enolates due to their limited availability, nonetheless, development of the synthetic utility of tin enolates has progressed because of their efficient chemo- and stereoselec-tivities. These reactions proceed without the use of any other catalysts such as transition-metals or Lewis acids. The general procedures using tin enolates are mainly based on stoichiometric reactions.[1] This background shows why the development of a system employing catalytic tin enolates is in high demand.[2] We investigated the catalytic use of tin enolates generated by the hydrostanation of enones with dibutylhalogenotin hydride (Bu_2SnClH or Bu_2SnIH), leading to the reductive aldol reaction of enones.[3] For the tin-catalyzed reductive aldol reactions, an equimolar amount of hydrosilane was essential in the regeneration of the tin hydride.[3b] Herein, we describe a tin-catalyzed cycloaddition of α-hydroxy ketones with 1,1-dicyanoalkenes to produce 2-amino-3-cyano-4,5-dihydrofurans **3**. The corresponding reaction was highly atom economical.[4] In this reaction, tin enolates were generated efficiently as active catalytic species without using any other metal species.

Results and discussion

Initially, the reaction of α-hydroxy acetone (**1a**) with 1,1-dicyanoalkene (**2a**) was examined (Table 1). Without a catalyst, no reaction proceeded at 25 °C for 24 h. In the presence of a tin(II) bis(2-ethylhexanoate)-MeOH system [$Sn(Oct)_2$-2MeOH] (10 mol%),[5] 2-amino-3-cyano-4-phenyl-5-acetyl-4,5-dihydrofuran (**3a**) was obtained as an adduct in a 39% yield (entry 1). The product **3a** was derived from the addition of an α-carbon of **1a** to **2a**. This feature contrasted with previously reported reaction with isocyanates by Tamariz[6a-d] and our groups,[6e] in which the product was derived from the addition of an OH group of **1a**.

Although the yield of **3a** at rt was insufficient (entry 1), the reaction under microwave irradiation gave **3a** in a higher yield (75%) within 10 min (entry 2). In contrast, using a $Bu_2Sn(OMe)_2$ catalyst resulted in a lower yield, for which a complex mixture was obtained (entry 3). Thus $Sn(Oct)_2$/MeOH was revealed to be a superior catalyst. Using excess amounts (2 equiv) of **1a** increased the yield of **3a** to 90% (entry 4). Among solvents examined (entries 5-8), MeCN was the best choice (entry 8). Product **3a** was also obtained under heating conditions at 80°C for 2 h (entry 9).

Table 1 Optimization of conditions[a]



Entry	Catalyst	**1a** (mmol)	Solvent	Conditions	Yield of **3a**	dr
1	$Sn(Oct)_2$-2MeOH	1	THF	25 °C, 24 h	39	74:26
2	$Sn(Oct)_2$-2MeOH	1	THF	MW, 94 °C	75	73:27
3	$Bu_2Sn(OMe)_2$	1	THF	MW, 97 °C	24	58:42
4	$Sn(Oct)_2$-2MeOH	2	THF	MW, 111 °C	90	71:29
5	$Sn(Oct)_2$-2MeOH	2	Hexane	MW, 95 °C	81	58:42
6	$Sn(Oct)_2$-2MeOH	2	DCE	MW, 117 °C	67	66:34
7	$Sn(Oct)_2$-2MeOH	2	Et_2O	MW, 95 °C	84	61:39
8	$Sn(Oct)_2$-2MeOH	2	MeCN	MW, 97 °C	96	67:33
9	$Sn(Oct)_2$-2MeOH	2	MeCN	80 °C [b]	86	58:42

[a] Reaction conditions: **2a** (2 mmol), cat. (0.1 mmol), solvent (1 mL), MW 30W, 10 min. [b] oil bath 2 h.

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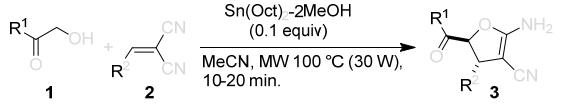
†Electronic Supplementary Information (ESI) available: Spectroscopic data including minor products.

Next, the reactions were carried out using various α-hydroxy ketones **1** with 1,1-dicyanoalkenes **2** catalyzed by $Sn(Oct)_2$/MeOH under optimized conditions (Table 2). The 1,1-dicyano alkenes **2a**-**2g** were reactive with **1a** to give **3a**-**3g** (entries 1-7). Various functionalities such as methoxy- and halogen substituents could be introduced on the aromatic rings of **2b**-**e** (entries 2-5). Naphtyl- and heterocyclic substituents were also introduced to products **3f** and **3g** (entries 6 and 7). Besides aromatic alkenes, an aliphatic version **2h** was also reactive to give the corresponding adduct **3h** (entry 8). In place of **1a**, the reaction using α-hydroxy acetophenone (**1b**) gave the corresponding adducts **3i**-**3k** effectively (entries 9-11). These products version of **3** included diastereoisomers, in which *trans*-substituted versions predominated. When α-hydroxy pinacolone (**1c**) was used, the corresponding cyclic products **3l**-**3s** were obtained effectively (entries 12-19). It is noteworthy that the *trans*-selectivities of **3l**-**3s** that were derived from **1c** were higher than those of **3a**-**3k** derived from the reactions using **1a** and **1b**. We tried to use cinnamyl nitrile as a simple Michael acceptor. However, no desired product was obtained. Perhaps doubly activated acceptor was needed.

Table 2 Cycloaddition of **1** with 1,1-dicyanoalkenes **2**[a]



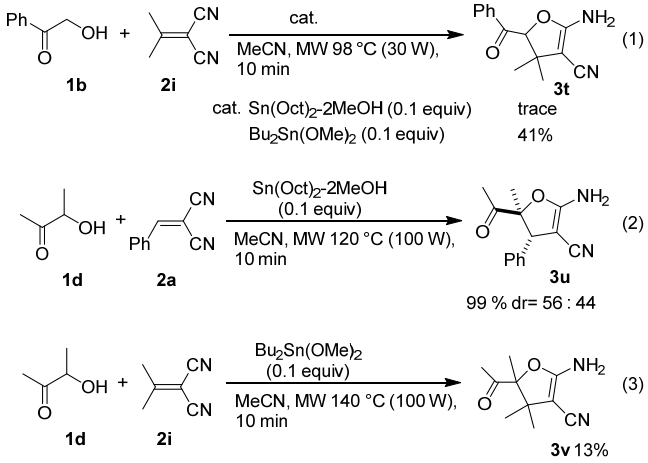
1 2 3

Entry	R^1	R^2	**3**	Yield of **3** (%)[f]	dr (*trans*:*cis*)
1	Me (**1a**)[b,c]	Ph (**2a**)	**a**	96	67:33
2		*p*-ClC_6H_4 (**2b**)	**b**	76	87:13
3		*p*-FC_6H_4(**2c**)	**c**	73	78:22
4		*p*-Tol (**2d**)	**d**	50	69:31
5		PMP (**2e**)	**e**	47	70:30
6		Np (**2f**)	**f**	91	67:33
7		furyl (**2g**)	**g**	64	66:34
8		$PhCH_2CH_2$ (**2h**)	**h**	48	83:17
9	Ph (**1b**)[c]	Ph (**2a**)	**i**	99	72:28
10		*p*-ClC_6H_4 (**2b**)	**j**	98	72:28
11		Np (**2f**)	**k**	70	70:30
12	*t*-Bu (**1c**)[d]	Ph (**2a**)	**l**	90	91:9
13		*p*-ClC_6H_4 (**2b**)	**m**	90	92:8
14		*p*-FC_6H_4 (**2c**)	**n**	64	89:11
15		*p*-Tol (**2d**)	**o**	52[e]	90:10
16		PMP (**2e**)	**p**	40[e]	90:10
17		Np (**2f**)	**q**	86	91:9
18		furyl (**2g**)	**r**	66	86:14
19		$PhCH_2CH_2$ (**2h**)	**s**	50	92:8

[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol), MeCN (1 mL), $Sn(OCOC_7H_{17})_2$ (0.1 mmol), [b] **1** (2 mmol), [c] 10 min, [d] 20 min, [e] 160 °C, [f] Determined by ^1H NMR based on **2.**

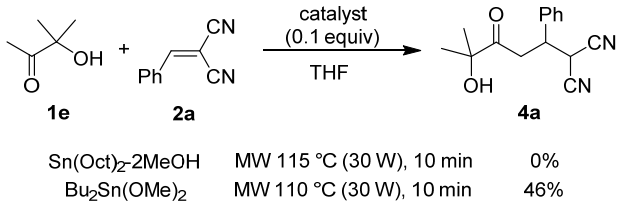
2-Amino-3-cyano-4,5-dihydrofurans are valuable synthetic intermediates for the preparation of pyrimidines,[7a-c] 2-pyrrolidinones,[7d,e] furopyridines,[7f] γ-butyrolactones,[7d,g] etc. Methods for the synthesis of 2-amino-3-cyano-4,5-dihydrofurans are limited.[4,8] The presented method requires only a small amount of base, and has wide applicability to aliphatic and aromatic alkenes and α-hydroxyl ketones.

As shown in Scheme 1, when *tetra*-substituted alkene **2i** was used as a substrate, a $Sn(Oct)_2$/MeOH catalyst afforded no products due to the steric hindrance of **2i**. However, $Bu_2Sn(OMe)_2$ was employed as an effective catalyst to give poly-substituted product **3t** with a quaternary carbon (eq. 1). Secondary alcohol **1d** also reacted effectively under the same conditions to give poly-substituted product **3u** with a quaternary carbon (eq. 2). Although the yield was less, even the combination between sterically hindered substrates **1d** and **2i** was allowed to give poly-substituted product **3v** with no protons on the ring (eq. 3).



Scheme 1

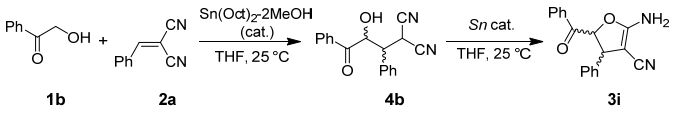
Tertiary alcohol **1e**, which has neither α-hydroxymethylene- nor α-hydroxymethine protons, gave no products when catalyzed by $Sn(Oct)_2$/MeOH. On the contrary, when $Bu_2Sn(OMe)_2$ was used as a catalyst, a linear type of adduct, **4a**, was obtained by the coupling of the tin enolate derived from an acetyl group of **1e** (Scheme 2). Thus, $Bu_2Sn(OMe)_2$ bears a higher basicity[9] than the $Sn(Oct)_2$/MeOH system which could not abstract acetyl protones.[10] As described in Table 1, in the reaction of **1a**, which possesses two types of acidic protons such as acetyl and α-hydroxymethylene groups, $Sn(Oct)_2$/MeOH was employed as a highly chemoselective catalyst to react only with α-hydroxymethylene or α-hydroxymethine protons.[11]

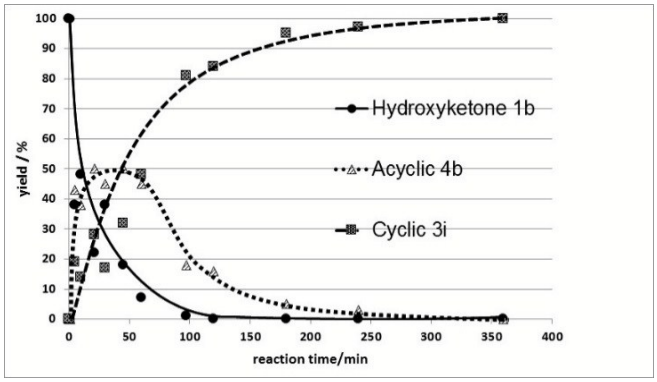


Scheme 2

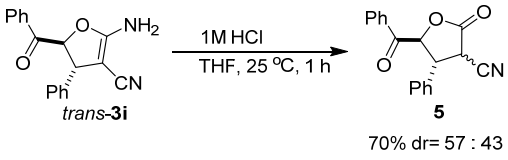
The reaction was monitored using α-hydroxy acetophenone (**1b**) with **2a** (Fig. 1). Products **4b** and **3i** were determined by ^{1}H NMR. Under the mild conditions at room temperature, the reaction took 360 minutes to attain a quantitative yield of cyclic product **3i**. The starting substrate **1b** decreased gradually with the reaction time and disappeared completely within 180 minutes. At the initial stage, a linear type of adduct, **4b**, was formed, and the yield was increased to 50% in 50 minutes. After 50 minutes, the yield of **4b** decreased. Hence, it was assumed that cyclic **3i** was formed through the linear adduct **4b**. We also confirmed that stirring of the THF solution of isolated **4b** for 6 h without a tin catalyst afforded no **3i**. Therefore, tin-catalysts were essential for the cyclization of **4b** to **3i**. Of course, there is a possibility that cyclic products **3** were formed directly without the passage of linear adducts **4**, particularly under severe conditions such as MW irradiation.

Fig. 1 Reaction profile of **1b** with **2a**



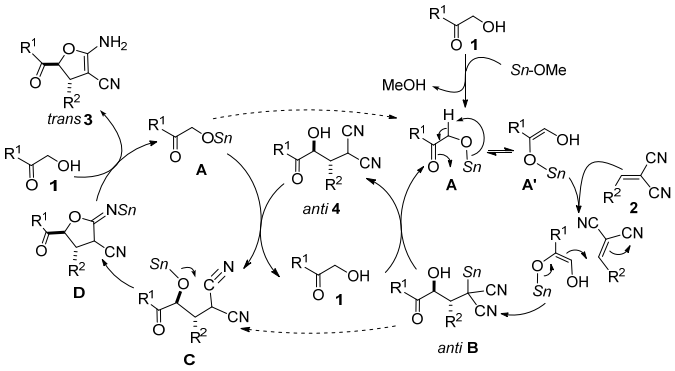


The cycloadducts of **3** include enamine structures in the ring. Although the products of **3** were isolated as stable compounds, the acid hydrolysis of **3i** easily led to α-cyano-γ-butyrolactone **5** (Scheme 3).[7g]



Scheme 3

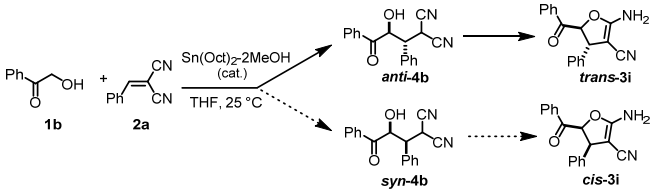
A plausible catalytic cycle forming major products *trans*-**3** is shown in Scheme 4. It is apparent that Sn-O and Sn-N bonds bear highly nucleophilic characteristics.[12] Initially, tin methoxide reacted with α-hydroxy ketone **1** to form α-stannoxy ketone **A**[13] which was in equilibrium with tin enolate **A'**. Next, the enolate carbon of **A'** was added to 1,1-dicyanoalkene **2** to form adduct **B**. Adduct **B** was protonated by starting α-hydroxy ketone **1**, and a linear adduct **4** was obtained with the regeneration of **A**. During cyclization, **4** was again stannylated by **A** to give tin alkoxide **C**, which was added to the remaining CN group intramolecularly. The Sn–N bond of cyclized product **D** was protonated by the initial **1**. As a result, cyclic product **3** was obtained and rearranged to an enamine structure, and catalytic species **A** was regenerated. Of course, a catalytic cycle without the passage of **4** was possible, in which tin alkoxide **C** was formed by an intramolecular tin-exchange from **B** (dotted line).

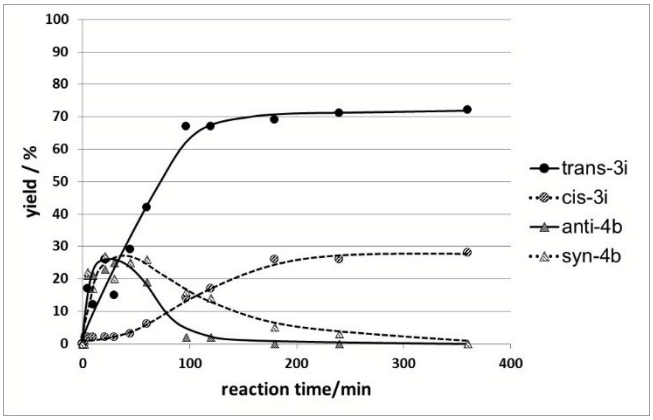


Scheme 4

The products of **3** obtained here include diastereoisomers. In the reaction of **1b** with **2a**, the formation of each diastereomer was also monitored (Fig. 2). It was cleared that the formation of *anti*-**4b** followed by *trans*-**3i** is faster than that of *syn*-**4b** to *cis*-**3i**.

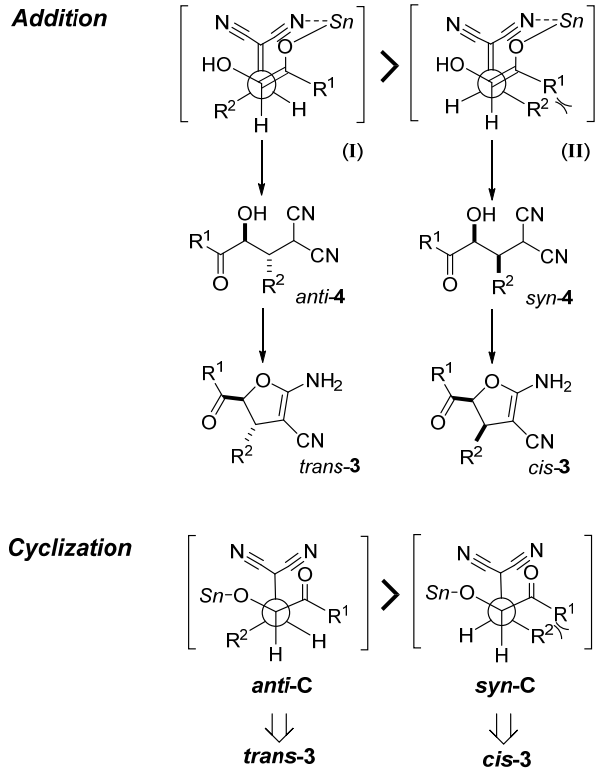
Fig. 2 Reaction profile for the formation of diastereo isomers





The *trans*-selectivity of **3** was dependent upon the substituent R^1 of α-hydroxy ketones **1**. Namely, a bulky R^1 substituent such as a *t*-Bu group underwent highly *trans*-selective reactions (Table 2, entries 10-19). The main diastereomeric product *trans*-**3** was formed *via anti*-**4**. The *anti*-selectivity of **4** was determined during C-C bond formation between tin enolate **A'** and dicyanoalkene **2**. The *in situ*-generated tin enolate **A'** is considered to be the *Z*-form because of the interaction of the tin center with an OH group.[14] In addition, a bulky R^1 group would increase the *Z*-selectivity. A plausible transition

state would be an eight-member cyclic transition state (Heathcock's model)[14,15] (Scheme 5). For the large *t*-Bu group (R^1) on the enolate, a transition structure (**I**) leading to *anti*-adduct **4** is favored over TS (**II**) in consideration of steric repulsion between R^1 and R^2. The effect was significant especially for the case of large R^1 such as *t*-Bu group. After the Michael addition, in the cyclization step, the course from *anti*-**C** to *trans*-**3** is also favored over the *syn*-**C** to *cis*-**3** in consideration of steric repulsion between R^1 and R^2.



Scheme 5

Conclusions

We demonstrated the catalytic conversion of 2-hydroxy ketones **1** to 2-amino-3-cyano-4-acyl-4,5-dihydrofurans **3** via a 1,3-dipolar cycloaddition. $Sn(Oct)_2$/MeOH was employed as an effective catalyst. The system employing catalytic tin enolate could be developed without the use of other metal reagents.

Experimental section

General information

Infrared spectra were recorded as thin film on a Nicolet iS5 spectrometer. All ^1H and ^{13}C NMR spectra were recorded with a JEOL JMTC-400/54/SS (400 and 100 MHz, respectively) in deuteriochloroform ($CDCl_3$) containing 0.03% (w/v) of tetramethylsilane as internal standard. Mass spectra were recorded on a JEOL JMS-DS-303 spectrometer. Flash column chromatography was performed by YAMAZEN YFLC-AI-580 using Hi-Flash Silica gel 2L Hi-Flash Column 20-3-mL/min eluted by Hexane/EtOAc with gradation mode changing from 9/1 to 3/7. Purification of products by recycle GPC system was performed by Japan Analytical Ind. LC-908 eluted by $CHCl_3$.

Di-*n*-butyltin dimethoxide [$^nBu_2Sn(OMe)_2$] was prepared according to the reported method using $^nBu_2SnO$ and dimethyl carbonate.[16] $Sn(OCOC_7H_{17})_2$ was purchased from Nakarai Tesque Co., Ltd. Substrates **1a**-**1e** were commercially available.

All reactions were carried out under dry nitrogen. Microwave assisted reactions were carried out using a focused microwave unit (CEM Discover microwave). The instrument consists of a continuous focused microwave power delivery system with operator selectable power output from 0-300 W. In all experiments, a constant power was applied to ensure reproducibility. Reactions were performed in glass vessels (10 mL) sealed with a septum. Pressure experiment is accomplished by a non-invasive sensor integrated into the cavity lid, which measures the deformation of the Teflon seal of the vessels (maximal 20 bar). Temperature controlled is achieved by means of an IR sensor and the indicated temperature corresponds to the maximal temperature reached during each experiment. The specified reaction time corresponds to the total irradiation time. Efficient cooling is accomplished by means of a pressurized air during the entire experiment.

General procedure for the preparation of product 3 under microwave irradiation. (Table 1, entry 8)

A 5 mL of vial was dried by flame under reduced pressure. After nitrogen was filled, Tin catalyst $Sn(OCOC_7H_{17})_2$ (0.0405 g, 0.1 mmol), MeOH (0.0064 g, 0.2 mmol), MeCN (1.0 mL), □-hydroxy acetone (**1a**) (0.148g, 2 mmol) and benzalmalononitrile (**2a**) (0.154g, 1 mmol) were added. The vial was sealed with a septum and was set in microwave reactor. The mixture was stirred under microwave irradiation at 30W for 10 min. The reaction temperature was measured by an IR sensor. After the reaction, the mixture was quenched by H_2O (0.5 mL), diluted with ether (10 mL) and the layers were quickly separated. The aqueous phase was further extracted with ether (5 mL x3), and the combined extracts were dried over sodium sulfate and concentrated. The yield of **3a** and the *trans*:*cis* selectivity was determined by ^1H NMR (0.110 g, 96%, *trans*:*cis*= 67:33). The crude product was then purified by flash column chromatography eluted by Hexane/EtOAc with gradation mode changing from 9/1 to 5/5. The desired product was obtained at Hexane/EtOAc=7:3. Spectral data for major products (*trans*-**3**) are listed as follows. Other minor products such as *cis*-**3** isomers are in ESI.

(4*S,5*S**)-5-Acetyl-2-amino-4-phenyl-4,5-dihydrofuran-3-carbonitrile** (***trans*-3a**)

Light brown solid, mp: 81-85 °C; IR (KBr) 3441, 2188, 1662 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.23 (s, 3H), 4.31 (d, J = 5.3 Hz, 1H), 4.72 (d, J = 5.3 Hz, 1H), 5.43 (s, 2H), 7.26-7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 50.4, 55.9, 92.0, 118.1, 127.0 , 127.9, 129.0, 140.8, 166.9, 204.4; MS (CI, *m*/*z*) 229 (M^++1, 100); HRMS (CI, *m*/*z*) calcd for $C_{13}H_{13}N_2O_2$ $[M+H]^+$ 229.0977, found 229.0978.

(4*S,5*S**)-5-Acetyl-2-amino-4-(4-chlorophenyl)-4,5-dihydrofuran-3-carbonitrile (*trans*-3b)**

Pale yellow wax, R_f= 0.33 (in hexane:ethyl acetate = 4:6); IR (neat) 3343, 2190, 1663 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.26 (s, 3H), 4.33 (d, *J*= 5.3 Hz, 1H), 4.66 (d, *J* = 5.3 Hz, 1H), 5.46 (s, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1, 49.9, 55.9, 91.9, 117.7, 128.5, 129.2, 133.7, 139.4, 166.9, 204.3; MS (CI, m/z) 263(M^++1, 100); HRMS (CI, *m/z*) calcd for $C_{13}H_{12}ClN_2O_2$ $[M+H]^+$ 263.0587, found 263.0580.

(4*S,5*S**)-5-Acetyl-2-amino-4-(4-fluorophenyl)-4,5-dihydrofuran-3-carbonitrile (*trans*-3c)**

Pale yellow wax, R_f= 0.66 (in hexane/ethyl acetate = 2:8); IR (neat) 3347, 2190, 1665) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 4.34 (d, *J* = 5.3 Hz, 1H), 4.67 (d, *J* = 5.3 Hz, 1H), 5.40 (s, 2H), 7.05 (t, *J* = 8.7 Hz, 2H), 7.27 (dd, *J* = 8.7, 5.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 49.8, 56.2, 92.1, 116.0 (d, *J* = 22.1 Hz), 117.8, 128.8 (d, *J* = 8.2 Hz), 136.6 (d, *J* = 3.3 Hz), 162.4 (d, *J* = 246.6 Hz), 166.8, 204.4; MS (CI, *m/z*) 247 (M^++1, 100); HRMS (CI, *m/z*) calcd for $C_{13}H_{12}FN_2O_2$ $[M+H]^+$ 247.0883, found 247.0881.

(*S,5*S**)-5-Acetyl-2-amino-4-(p-tolyl)-4,5-dihydrofuran-3-carbonitrile (*trans*-3d)**

Pale yellow wax, R_f= 0.75 (in hexane/ethyl acetate = 2:8); IR (neat) 3346, 2189, 1663 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3H), 2.33 (s, 3H), 4.28 (d, *J* = 5.6 Hz, 1H), 4.70 (d, *J* = 5.6 Hz, 1H), 5.33 (s, 2H), 7.10-7.25 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 26.0, 50.3, 56.5, 92.3, 117.9, 127.0, 129.7, 137.6, 137.8, 166.8 , 204.3; MS (CI, *m/z*) 243(M^++1, 100); HRMS (CI, *m/z*) calcd for $C_{14}H_{15}N_2O_2$ $[M+H]^+$ 243.1134, found 243.1137.

(4*S,5*S**)-5-Acetyl-2-amino-4-(4-methoxyphenyl)-4,5-dihydrofuran-3-carbonitrile (*trans*-3e)**

Pale yellow wax; R_f= 0.24 (in hexane:ethyl acetate = 4:6); IR (neat) 3347, 2188, 1667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 3.81 (s, 3H), 4.29 (d, *J* = 5.6 Hz, 1H), 4.70 (d, *J* = 5.6 Hz, 1H), 5.12 (s, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 7.21 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 50.0, 55.3, 57.2, 92.5, 114.5, 117.7, 128.2, 132.8, 159.3, 166.4, 204.2; MS (CI, *m/z*) 259 (M^++1, 100); HRMS (CI, m/z) calcd for $C_{13}H_{15}N_2O_3$ $[M+H]^+$ 259.1083, found 259.1079.

(4*S,5*S**)-5-Acetyl-2-amino-4-(naphthalen-2-yl)-4,5-dihydrofuran-3-carbonitrile (*trans*-3f)**

Pale orange solid, mp: 55 °C; IR (KBr) 3341, 2188, 1661 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H), 4.46 (d, *J* = 5.3 Hz, 1H), 4.74 (d, *J* = 5.3 Hz, 1H,), 5.48 (s, 2H), 7.37-7.79 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 50.7, 56.1, 91.9, 118.0, 124.7, 126.1, 126.1, 126.4, 127.6, 127.9, 129.2, 132.9, 133.3, 138.1, 167.0, 204.4; MS (CI, *m/z*) 279 (M^++1, 100); HRMS (CI, *m/z*) calcd for $C_{17}H_{15}N_2O_2$ $[M+H]^+$ 279.1134, found 279.1134.

(4*S,5*S**)-2'-Acetyl-5'-amino-2',3'-dihydro-[2,3'-bifuran]-4'-carbonitrile (*trans*-3g)**

Pale yellow solid, mp: 123 °C, IR (KBr) 3446, 2189, 1657 cm^{-1}; ^1H NMR (400 MHz) δ 2.28 (s, 3H), 4.43 (d, *J* = 4.8 Hz, 1H), 4.93 (d, *J* = 4.8 Hz, 1H), 5.34 (s, 2H), 6.30 (dd, *J* = 3.4, 0.7 Hz, 1H), 6.34 (dd, *J* = 3.4, 1.9 Hz, 1H), 7.40 (dd, *J* = 1.9, 0.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 43.9, 54.1, 88.8, 107.2, 110.6, 117.5, 142.8, 152.8, 166.9, 203.5; MS (CI, *m/z*) 219(M^++1, 100); HRMS (CI, *m/z*) calcd for $C_{11}H_{11}N_2O_3$ $[M+H]^+$ 219.0770, found 229.0771.

(4*S,5*S**)-5-Acetyl-2-amino-4-phenethyl-4,5-dihydrofuran-3-carbonitrile (*trans*-3h)**

Pale yellow liquid, R_f= 0.49 (in hexane:ethyl acetate = 4:6); IR (neat) 3342, 2185, 1663 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.86-2.06 (m, 2H), 2.20 (s, 3H), 2.75 (t, *J* = 8.0 Hz, 2H), 3.16-3.21 (m, 1H), 4.55 (d, *J* = 4.8 Hz, 1H), 4.98 (s, 2H), 7.15-7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7, 32.2, 37.4, 45.0, 56.3, 89.9, 118.2, 126.1, 128.4, 128.5, 140.8, 166.3, 205.4; MS (EI, *m/z*) 256 (M^+, 18), 109(100), 91(55), 43(41); HRMS (EI, *m/z*) calcd for $C_{13}H_{16}N_2O_2$ 256.1212, found 256.1213.

(4*S,5*S**)-2-Amino-5-benzoyl-4-phenyl-4,5-dihydrofuran-3-carbonitrile (*trans*-3i)**

Light brown solid, mp: 145-150 °C; IR (KBr) 3432, 2191, 1670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.33 (d, *J* = 4.8 Hz, 1H), 5.46 (s, 2H), 5.68 (d, *J* = 4.8 Hz, 1H), 7.25 (d, *J* = 7.0 Hz, 2H), 7.32-7.36 (m, 3H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.77 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.9, 56.9, 89.0, 118.1, 127.4, 128.1 , 128.8 , 128.9, 129.1, 133.1, 134.2, 140.9, 167.2, 193.0; MS (CI, m/z) 291(M^++1, 100); HRMS (CI, m/z) calcd for $C_{18}H_{15}N_2O_2$ $[M+H]^+$ 291.1134, found 291.1130.

(4*S,5*S**)-2-Amino-5-benzoyl-4-(4-chlorophenyl)-4,5-dihydrofuran-3-carbonitrile (*trans*-3j)**

Pale yellow solid, mp: 130-132 °C; IR (KBr) 3396, 2184, 1660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$,) δ 4.39 (d, *J* = 4.8 Hz, 1H), 5.03 (2H, s, g), 5.64 (d, *J* = 4.8 Hz, 1H), 7.22-7.26 (m, 2H), 7.32-7.36 (m, 2H), 7.42 (d, *J* = 7.7 Hz, 2H), 7.62-7.65 (m, 1H), 7.79 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.2, 56.7, 88.8, 117.7, 128.7, 128.8, 128.9, 129.3, 133.1, 133.9, 134.4, 139.3,167.2, 192.6; MS (CI, m/z) 325(M^++1, 100); HRMS (CI, m/z) calcd for $C_{18}H_{14}ClN_2O_2$ $[M+H]^+$ 325.0774, found 325.0776.

(4*S,5*S**)-2-Amino-5-benzoyl-4-(naphthalen-2-yl)-4,5-dihydrofuran-3-carbonitrile (*trans*-3k)**

Pale yellow solid, mp: 140-142°C; IR (KBr) 3325, 2180, 1656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.54 (d, *J* = 4.8 Hz, 1H), 5.02 (s, 2H), 5.81 (d, *J* = 4.8 Hz, 1H), 7.41-7.59 (m, 5H), 7.59-7.67 (m, 2H), 7.80-7.92 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.1, 56.8, 88.7, 118.1, 124.7, 126.1, 126.3, 126.5, 127.6, 127.8, 128.7, 128.8, 128.9, 129.3 133.0, 133.2, 134.1, 138.0, 167.3, 193.0; MS (CI, m/z) 341(M^++1, 100); HRMS (CI, m/z) calcd for $C_{22}H_{17}N_2O_2$ $[M+H]^+$ 341.1290, found: 341.1291.

(4*S,5*S**)-2-Amino-4-phenyl-5-pivaloyl-4,5-dihydrofuran-3-carbonitrile (*trans*-3l)**

White solid, mp: 199-202 °C; IR (neat) 3420, 2196, 1672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (s, 9H), 4.30 (d, *J* = 5.3 Hz, 1H), 4.94 (s, 2H), 5.18 (d, *J* = 5.3 Hz, 1H), 7.26-7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 43.5, 51.0, 58.11, 87.9, 117.8, 127.3, 128.0, 129.1, 140.8, 166.5, 208.6; MS (CI, *m/z*) 271(M^++1, 100); HRMS (CI, *m/z*) calcd for $C_{16}H_{19}N_2O_2$ $[M+H]^+$ 271.1447, found 271.1448.

(4*S,5*S**)-2-Amino-4-(4-chlorophenyl)-5-pivaloyl-4,5-dihydrofuran-3-carbonitrile (*trans*-3m)**

White solid, mp: 145-148°C; IR (neat) 3337, 2187, 1659 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (s, 9H), 4.31 (d, *J* = 5.3 Hz, 1H), 5.09 (d, *J* = 5.3 Hz, 1H), 5.48 (s, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 43.5, 50.2, 56.4, 87.7, 118.0, 128.7, 129.1, 133.5, 139.5, 167.0, 208.8; MS (EI, *m/z*) 304 (M^+, 4), 247 (100), 57 (35); HRMS (EI, *m/z*) calcd for $C_{16}H_{17}ClN_2O_2$ 304.0979, found 304.0973.

(4*S,5*S**)-2-Amino-4-(4-fluorophenyl)-5-pivaloyl-4,5-dihydrofuran-3-carbonitrile (*trans*-3n)**

White solid, mp: 206-207 °C; IR (neat) 3419, 2195, 1672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 9H), 4.33 (d, *J* = 5.6 Hz, 1H), 4.92 (s, 2H), 5.11 (d, *J* = 5.6 Hz, 1H), 7.06 (t, *J* = 8.7 Hz, 2H), 7.25 (dd, *J* = 8.7, 5.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 43.6, 50.3, 58.1, 88.0,

116.0 (d, *J* = 22.1 Hz), 117.5, 129.0 (d, *J* = 8.2 Hz), 136.5 (d, *J* = 3.3 Hz), 161.2, 166.4, 208.5; MS (EI, *m/z*) 288 (M^+, 6), 231 (100); HRMS (EI, *m/z*) calcd for $C_{16}H_{17}FN_2O_3$ 288.1274, found 288.1273.

(4*S,5*S**)-2-Amino-5-pivaloyl-4-(p-tolyl)-4,5-dihydrofuran-3-carbonitrile (*trans*-3o)**

White solid, mp: 143-145 °C; IR (neat) 3428, 2186, 1666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (s, 9H), 2.34 (s, 3H), 4.25 (d, *J* = 5.3 Hz, 1H), 5.07 (s, 2H), 5.15 (d, *J* = 5.3 Hz, 1H), 7.16-7.23 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 26.0, 43.5, 50.7, 57.9, 87.9, 118.0, 127.2, 129.7, 137.6, 137.9, 166.7, 208.8; MS (EI, *m/z*) 284 (M^+, 5), 227 (100), 57 (28), 43 (26); HRMS (EI, *m/z*) calcd for $C_{17}H_{20}N_2O_2$ 284.1525, found 284.1521.

(4*S,5*S**)-2-Amino-4-(4-methoxyphenyl)-5-pivaloyl-4,5-dihydrofuran-3-carbonitrile (*trans*-3p)**

White solid, mp: 162-163 °C; IR (neat) 3423, 2193, 1670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (s, 9H), 3.81 (s, 3H), 4.26 (d, *J* = 5.6 Hz, 1H), 4.91 (s, 2H), 5.14 (d, *J* = 5.6 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 7.19 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 43.5, 50.5, 55.3, 58.4, 88.0, 114.4, 117.8, 128.5, 132.8, 159.3, 166.4, 208.7; MS (EI, *m/z*) 300 (M^+, 5), 243 (100), 57 (29); HRMS (EI, *m/z*) calcd for $C_{17}H_{20}N_2O_3$ 300.1474, found: 300.1476.

(44*S,5*S**)-2-Amino-4-(naphthalen-2-yl)-5-pivaloyl-4,5-dihydrofuran-3-carbonitrile (*trans*-3q)**

Pale yellow solid, mp: 169-173 °C; IR (neat) 3418 (NH_2), 2197 (CN), 1665 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (s, 9H), 4.47 (d, *J* = 5.3 Hz, 1H), 5.21 (s, 2H), 5.25 (d, *J* = 5.3 Hz, 1H), 7.40 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.46-7.49 (m, 2H), 7.70 (d, *J* = 1.7 Hz, 1H), 7.82 (m, 2H), 7.86 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 43.5, 51.2, 57.5, 87.7, 118.0, 124.8, 126.1, 126.4, 126.4, 127.7, 127.9, 129.2, 133.0, 133.3, 138.1, 166.8, 208.8; MS (EI, *m/z*) 320(M^+, 4), 263(48), 57(28), 43(100); HRMS (EI, *m/z*) calcd for $C_{20}H_{20}N_2O_2$ 320.1525, found 320.1523.

(4*S,5*S**)-5'-Amino-2'-pivaloyl-2',3'-dihydro-[2,3'-bifuran]-4'-carbonitrile (*trans*-3r)**

White solid, mp: 114-117 °C; IR (neat) 3327, 2181, 1656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 9H), 4.40 (d, *J* = 5.1 Hz, 1H), 5.35 (d, *J* = 5.1 Hz, 1H), 5.40 (s, 2H), 6.28 (dd, *J* = 3.1, 1.0 Hz, 1H), 6.34 (dd, *J* = 3.1, 1.9 Hz, 1H), 7.39 (dd, *J* = 1.9, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 43.5, 44.2, 53.8, 84.1, 107.3, 110.5, 117.9, 142.5, 152.9, 167.3, 208.5; MS (EI, *m/z*) 271 (M^+, 4), 203 (100), 57 (81); HRMS (EI, *m/z*) calcd for $C_{16}H_{19}N_2O_2$ 260.1161, found 260.1160.

(4*S,5*S**)-2-Amino-4-phenethyl-5-pivaloyl-4,5-dihydrofuran-3-carbonitrile (*trans*-3s)**

White solid, mp: 120-122 °C; IR (neat) 3403, 2183, 1668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 9H), 1.89-2.05 (m, 2H), 2.66-2.85 (m, 2H), 3.20 (dt, *J* = 7.0, 4.8 Hz, 1H), 4.90 (d, *J* = 4.8 Hz, 1H), 5.16 (s, 2H), 7.16-7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1, 32.0, 37.2, 43.4, 44.5, 55.3, 86.3, 118.9, 126.0, 128.4, 128.4, 141.0, 167.0, 209.2; MS (EI, *m/z*) 298 (M^+, 25), 241 (92), 130 (27), 109 (42), 91 (97), 57 (100); HRMS (EI, *m/z*) calcd for $C_{18}H_{22}N_2O_2$ 298.1681, found 298.1683.

2-Amino-5-benzoyl-4,4-dimethyl-4,5-dihydrofuran-3-carbonitrile (3t)

White solid, mp: 191-194 °C; IR (KBr) 3401, 2173, 1661 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 3H), 1.46 (s, 3H), 4.86 (s, 2H), 5.64 (s, 1H), 7.52 (t, *J* = 7.7 Hz, 2H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.89 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0, 28.7, 46.6, 54.1, 90.8, 117.4, 128.4, 129.0, 134.1, 135.9, 164.9, 194.3; MS (EI, *m/z*) 242(M^+, 9), 227 (10), 137 (10), 105 (100), 77 (22); HRMS (EI, *m/z*) calcd for $C_{14}H_{14}N_2O_2$ 242.1055, found 242.1056.

(4*S,5*S**)-5-Acetyl-2-amino-5-methyl-4-phenyl-4,5-dihydrofuran-3-carbonitrile (*trans*-3u)**

Pale yellow wax, R_f= 0.45 (in hexane/ethyl acetate = 5:5); IR (neat) 3345, 2190, 1662 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 3H), 2.26 (s, 3H), 4.41 (s, 1H), 5.68 (s, 2H), 7.19-7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 24.9, 52.6, 55.0, 95.1, 118.5, 127.7, 128.4, 128.4, 137.2, 166.8, 209.8; MS (EI, *m/z*) 242 (M^+, 100); HRMS (EI, *m/z*) calcd for $C_{14}H_{14}N_2O_2$ 242.1055, found 242.1054.

5-Acetyl-2-amino-4,4,5-trimethyl-4,5-dihydrofuran-3-carbonitrile (3v)

White solid, mp: 177-178 °C; IR (KBr) 3398, 2175, 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 3H), 1.26 (s, 3H), 1.39 (s, 3H), 2.28 (s, 3H), 4.70 (s, 2H); MS (EI, *m/z*) 194 (M^+,28), 179 (27), 151 (38), 137 (100), 43 (37); HRMS (EI, *m/z*) calcd for $C_{10}H_{14}N_2O_2$ 194.1055, found 194.1054.

2-((1*R,2*S**)-2-Hydroxy-3-oxo-1,3-diphenylpropyl)malononitrile (4b Major)**

This product was isolated from the reaction mixture by flash column chromatography eluted by Hexane/EtOAc= 7/3. Further purfication was performed by GPC eluted with $CHCl_3$.

White wax, R_f= 0.45 (in hexane:ethyl acetate = 8:2); IR (neat) 2189, 1687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.77 (dd, *J* = 11.6, 2.7 Hz, 1H), 4.05 (d, *J* = 6.0 Hz, 1H), 4.57 (d, *J* = 11.6 Hz, 1H), 5.63 (dd, *J* = 6.0, 2.7 Hz, 1H), 6.84 (d, *J* = 7.4 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 2H), 7.73 (t, *J* = 7.5 Hz, 1H), 7.77 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1, 50.7, 72.2, 111.5, 112.3, 128.1 , 128.4, 129.0, 129.4, 129.6, 130.9, 133.1, 134.9, 197.2; MS (EI, *m/z*) 290 (M^+, 4), 225 (10), 105 (100), 77 (24); HRMS (EI, *m/z*) calcd. for $C_{18}H_{14}N_2O_2$ 290.1055, found 290.1050.

5-Benzoyl-2-oxo-4-phenyltetrahydrofuran-3-carbonitrile (diastereomers mixture) (**5**)

THF (1 mL) solution of **3i** (0.087g, 0.3 mmol) with 1M HCl (2 mL) was stirred at 25 °C for 1 h. After the reaction, the mixture was extracted with ether (5 mL x3), and the combined extracts were dried over sodium sulfate and concentrated. The yield of **5** was determined by ^1H NMR (0.061 g, 70%). The crude product was then purified by flash column chromatography eluted by Hexane/EtOAc with gradation mode changing from 9/1 to 5/5. The desired product was obtained at Hexane/EtOAc=5:5.

Clear wax; R_f= 0.69 (in hexane:ethyl acetate = 5:5); IR (neat), 2257, 1794, 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (Major) δ 4.07 (d, *J* = 10.9 Hz, 1H), 4.39 (dd, *J* = 10.9, 8.5 Hz, 1H), 5.75 (d, *J* = 8.5 Hz, 1H), 7.32-7.93 (m, 10H). (Minor) δ 4.10 (dd, *J* = 1.2, 8.7 Hz, 1H), 4.27 (d, *J* = 8.7 Hz, 1H), 6.04 (d, *J* = 1.2 Hz, 1H), 7.32-7.93 (m, 10H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 37.8, 39.7, 46.2, 47.8, 82.1, 82.7, 112.3, 113.7, 127.1, 127.3, 128.8, 129.0, 129.2, 129.3, 129.4, 129.6, 129.7, 129.9, 132.5, 133.7, 134.2, 134.8, 135.3, 135.5, 165.9, 167.5, 190.7, 192.3; MS (CI, *m/z*) 292 (M^++1, 100); HRMS (CI, *m/z*) calcd for $C_{18}H_{14}NO_3$ $[M+H]^+$ 292.0974, found 292.0976.

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