Pergamon

Tetrahedron Letters 42 (2001) 3563–3565

TETRAHEDRON LETTERS

Concise enantio- and diastereoselective synthesis of α-hydroxy-α-methyl-β-amino acids

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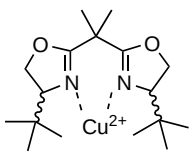
Received 22 December 2000; accepted 5 March 2001

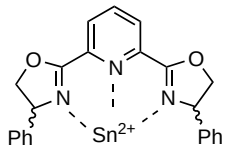
Abstract—Reported here is an efficient procedure for enantio- and diastereoselective synthesis of pure β-amino acids that display a *tert*-hydroxyl functionality in the α-position. Key steps include a catalytic asymmetric aldol reaction and a modified Curtius rearrangement to form oxazolidinone intermediates, which are chemoselectively opened to furnish *N*-protected α-hydroxy-α-methyl-β-amino acids. A modified work-up procedure of the aldol reaction allows for recovery of up to 90% of bisoxazolinyl ligands from the catalysts.

α-Hydroxy-β-amino acids constitute an important class of amino acids because of their occurrence in many biologically relevant compounds.[1] Representative examples are Paclitaxel (Taxol),[2] a clinically significant anticancer agent, and the aminopeptidase inhibitors bestatin[3] and amastatin.[4] Previous synthetic efforts towards α-hydroxy-β-amino acid substructures have used the Sharpless asymmetric aminohydroxylation of α,β-unsaturated amides,[5] Ojima's β-lactam ring-opening procedure,[6a] as well as microbial[7] or asymmetric catalytic reduction of α-keto carboxylic acid derivatives.[8] Some of these approaches are restricted in scope to secondary alcohols at the α-position or by insufficient enantio- or diastereoselectivity.[6b]

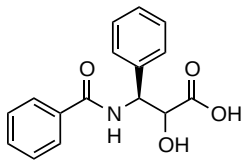
We report here a novel synthesis of β-amino acids **A** that display a tertiary hydroxyl group at the α-position. The present approach allows full control over both stereocenters in **A**. The starting point for the synthesis is a catalytic enantioselective aldol addition of enolsilanes to pyruvate esters (Scheme 1), recently reported by Evans and co-workers.[9]



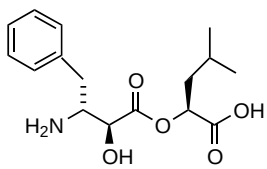
1a (S,S)
1b (R,R)



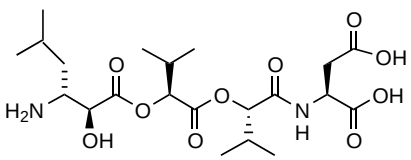
2a (S,S)
2b (R,R)



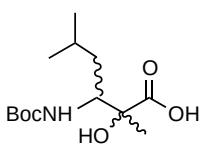
1, Paclitaxel side chain



2, Bestatin



3, Amastatin



A

Keywords: catalytic aldol; Curtius rearrangement; β-amino acid.

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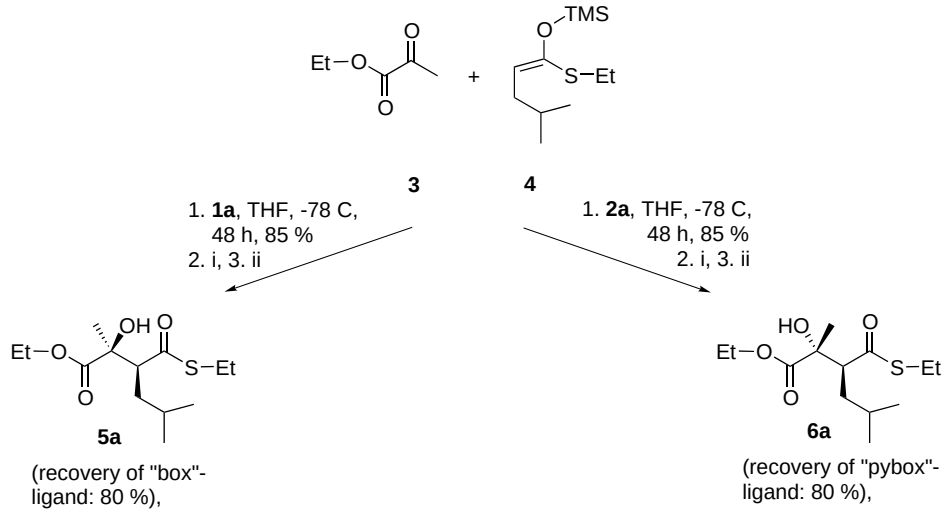
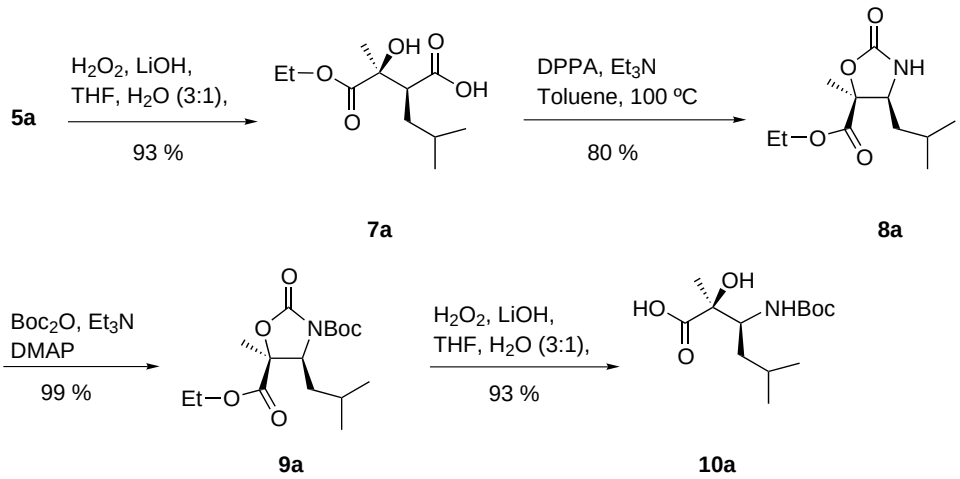


Scheme 1. Synthesis of the hydroxythioesters **5a** and **6a**. (i) aq. EDTA (0.5 M); (ii) HCl, THF.

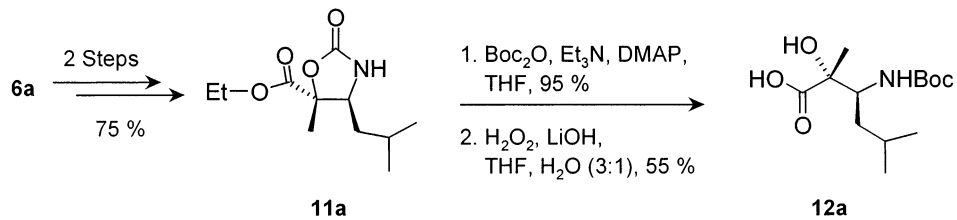
The C_2-symmetric bis(*tert*-butyl-oxazolinyl)Cu(OTf)$_2$ ('box') complexes **1a**,**b**[10] catalyze the addition of **4**[11] to **3** to give the *syn*-aldol product. The corresponding *anti*-aldol product **6a** is synthesized via a {bis(phenyl-oxazolinyl)pyridine}Sn(OTf)$_2$ ('pybox', **2a**) catalyzed reaction.[12]

Exclusive usage of Schlenck technique leads to diastereomeric ratios of 10:1–15:1, and the enantiopurity of the major diastereomer over 91% ee. In order to recover the ligands[13] we modified the typical work-up procedure: extraction of the reaction mixture with 0.5 M aq. EDTA (pH 8) allows complete sequestration of Sn(II) and Cu(II). The aldol products (before deprotection of the TMS unit) and ligands easily can then be separated by column filtration. This simple procedure typically leads to 80% ligand recovery for 'box' and 'pybox', respectively.

As shown in Scheme 2, the thioester in the aldol products can be selectively hydrolyzed using lithium hydroxide and hydrogen peroxide in aq. THF. In order to obtain complete conversion, it is important to use 3 equiv. of LiOH together with an 15-fold excess of



Scheme 2. Transformation of the *syn*-aldol adduct **5a** into the α-hydroxy β-amino acid **10a**.



Scheme 3. Transformation of the *anti*-aldol adduct **6a** into **12a**.

H_2O_2. Reaction of **7a** with DPPA leads to the oxazolidinone **8a** in 80% yield. The formation of the azide intermediate can be monitored by TLC at rt. Heating to 100°C completes the ring closure to form the carbamate. After Boc-protection of **8a** with di-*tert*-butyl dicarbonate the resultant oxazolidinone **9a** was hydrolyzed using LiOH in aq. THF to furnish the acid **10a** in 63% yield.[14]

Scheme 3 shows the analogous transformation of the *anti*-diastereomer **6a** into the corresponding α-hydroxy β-amino acid **12a**. The constitution and relative configuration of the two stereocenters of the oxazolidinone **11a** was confirmed by single-crystal X-ray analysis.[15] The final hydrolysis step leading to **12a** was observed to proceed more slowly than that of **9a** to **10a**.

The synthetic scheme presented here can be adopted for a general synthesis of substituted β-amino acids with diverse variations of the alkyl side chains.

Acknowledgements

R.R. is grateful to the Alexander-von-Humboldt Foundation (Germany) for financial support. This work was supported by a generous grant from Enanta Pharmaceuticals.

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Analytical data of *syn*-(2*S*,3*S*)-methyl-2,5-dimethyl-2-hydroxy-3-*tert*-butoxycarbonylamino-hexanoate prepared from (2*S*,3*S*)-2,5-dimethyl-2-hydroxy-3-*tert*-butoxycarbonylamino-hexanoic acid **10a**: IR 3391.0, 2956.7, 1715.0, 1504.1, 1366.9, 1255.5, 1166.3, 1045.9, 772.0 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.61 (d, 1H, $J=$ 10.4 Hz, NH), 3.92 (dd, 1H, $J=7.4$, 2 Hz, C**H**$CH_2CH(CH_3)_2$), 3.76 (s, 3H, $COOCH_3$), 3.48 (s, 1H, $C(CH_3)$**OH**, 1.60 (m, 1H, CH_2C**H**$(CH_3)_2$), 1.40 (s, 9H, C(**CH_3**$)_3$), 1.39 (m, 2H, **CH_2**$CH(CH_3)_2$), 1.36 (s, 3H, C(OH)**CH_3**), 0.92 (d, 6H, $J=6.8$ Hz, CH(**CH_3**$)_2$); ^{13}C NMR (100 MHz) δ 176.8, 157.2, 79.2, 78.2, 55.1, 53.0, 39.8, 28.5, 25.5, 23.9, 23.4, 21.4; LRMS (ES+) m/z 289 $(MH)^+$, 312 $(MNa)^+$, 353 (MNa+acetonitrile)$^+$; HRMS (ES+) exact mass calcd for $(C_{14}H_{27}NO_5+Na)^+$ requires m/z 312.1787; found m/z 312.1766.
(2*R*,3*S*)-Methyl-2,5-dimethyl-2-hydroxy-3-*tert*-butoxycarbonylamino-hexanoate from (2*S*,3*S*)-2,5-dimethyl-2-hydroxy-3-*tert*-butoxycarbonylamino-hexanoic acid **12a**: IR 3356.2, 2955.7, 1731.6, 1514.0, 1366.5, 1252.1, 1173.2, 1107.8 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.63 (d, 1H, $J=10.4$ Hz, NH), 3.97 (ddd, 1H, $J=16.4$, 7, 2.4 Hz, C**H**$CH_2CH(CH_3)_2$), 3.79 (s, 3H, $COOCH_3$), 3.23 (s, 1H, $C(CH_3)$**OH**, 1.63 (m, 2H, CH_2C**H**$(CH_3)_2$, **CH_2**CH-$(CH_3)_2$), 1.43 (s, 9H, C(**CH_3**$)_3$), 1.38 (s, 3H, C(OH)**CH_3**), 0.89 (d, 3H, $J=2$ Hz, CH(**CH_3**$)_2$), 0.87 (d, 3H, $J=2.4$ Hz, CH(**CH_3**$)_2$), 0.78 (ddd, 1H, $J=18$, 10.4, 2.4 Hz, **CH_2**$CH(CH_3)_2$), ^{13}C NMR (100 MHz) δ 176.9, 156.6, 79.2, 78.0, 55.7, 52.9, 38.2, 28.4, 25.4, 24.0, 22.9, 21.5; LRMS (ES+) m/z 289 $(MH)^+$, 312 $(MNa)^+$, 353 (MNa+acetonitrile)$^+$; HRMS (ES+) exact mass calcd for $(C_{14}H_{27}NO_5+Na)^+$ requires m/z 312.1787; found m/z 312.1797.
15. Roers, R.; Verdine, G. L., unpublished results.

Pergamon

Tetrahedron Letters 42 (2001) 3571–3573

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Selective preparation of (*Z*)- and (*E*)-prop-1-enylamides from *N*-allylbenzamides

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Received 27 March 2001; accepted 28 March 2001

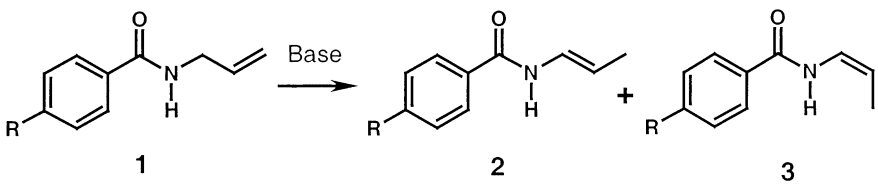
Abstract—A series of *para*-substituted *N*-allylbenzamides was submitted to isomerization under basic conditions. With LDA at −78°C, the corresponding (*E*)-*N*-(prop-1-enyl)benzamide was the major product. With *n*-butyllithium and the mixture warmed to 0°C, the (*Z*)-isomer was essentially furnished.

The directed *ortho*-metallation of arenes is a powerful method for the elaboration of complex aromatic compounds.[1] Although deprotonation of aromatic amides by alkyllithium and electrophilic capture of lithiated species is of particular interest for preparing *ortho*-substituted derivatives,[2] the major problems associated with the use of these *ortho*-directing groups are their great resistance to hydrolysis and the difficulty of their transformation to other useful functionalities.[3] Tischler reported base-induced isomerization of *N*-allylbenzamide **1a** to enamides that were easily hydrolyzed (Scheme 1).[4] Starting from benzamides **1** (R = H, OCH_3), Fisher and co-workers used 1:1 mixtures of (*Z*)- and (*E*)-*N*-(prop-1-enyl)benzamides to prepare isoquino-1(2*H*)-ones.[5]

During the study of the preparation substituted isoquinolones, we observed that isomerization of *para*-substituted benzamides **1b–e** under basic conditions gave mixtures of enamides **2** and **3** with ratios varying from about 3:2 to 1:9 (Scheme 1).[6] Herein, we report the results obtained for optimizing the stereoselectivity and yield of reaction.

Benzamide **1a** was used in a preliminary study and the results are summarized in Table 1. The lithiated derivatives were prepared by addition of a solution of **1a** in THF into a solution of LDA (2.2 equiv.) in THF at −78°C. After 5 min, the reaction mixture was allowed to warm (entries 1–3). At 0°C the mixture rapidly turned from a deep purple to a dark yellow color. ^{1}H NMR analysis of the mixture obtained after work-up indicates a quantitative isomerization of the allylamide to a 2:3 mixture of (*E*)- and (*Z*)-*N*-(prop-1-enyl)-benzamides (**2a** and **3a**).[7] When the reaction mixture was maintained at −78°C and quenched at this temperature with methanol (entries 4–7), the *E*/*Z* ratio remained essentially the same, with **2a** as the major product. Consequently, the isomerization was supposed to be the result of a relatively slow metallation reaction at −78°C.

Some experiments were conducted with *n*-butyllithium instead of LDA. A solution of *n*-butyllithium in hexane (2.2 equiv.) was added to a solution of benzamide **1a** in THF at −78°C; an intense color developed upon the addition of the second equivalent of base. When the



Scheme 1. Base: *n*-BuLi, *i*-Pr_2Li; R: **a** = H, **b** = CH_3, **c** = $CH(OMe)_2$, **d** = $C(OMe)_2CH_3$, **e** = $C(OMe)_2Ph$.

Keywords: lithiation; isomerization; allylbenzamides; enamides.

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Table 1. Isomerization of *N*-allylbenzamide **1a** to enamides **2a** and **3a**

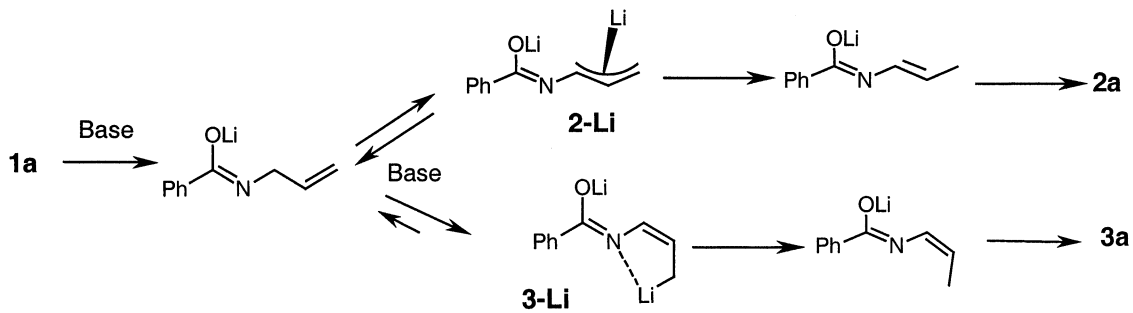
Entry	Base	Additive (equiv.)	Conditions °C (min)	Conversion[a] (%)	*E*/*Z* ratio[a] **2a**:**3a**
1	LDA		−78 (5), 0 (5)	100	40:60
2	LDA		−78 (5), −25 (90)	100	50:50
3	LDA		−78 (5), −40 (120)	100	60:40
4	LDA		−78 (5)[b]	26	76:24
5	LDA		−78 (45)[b]	69	74:26
6	LDA		−78 (120)[b]	85	80:20
7	LDA		−78 (240)[b]	97	78:22
8	*n*-BuLi		−78 (5)[b]	0	–
9	*n*-BuLi		−78 (120)[b]	25	10:90
10	*n*-BuLi		−78 (15), 0 (90), −78 (15)[b]	96 (75)[c]	7:93
11	*n*-BuLi		−78 (15), 0 (1)[b]	92	5:95
12	LDA	HDA[d] (20)	−78 (120)[b]	81	87:13
13	LDA	HDA[d] (20)	−78 (210)[b]	89	85:15
14	LDA	HDA[d] (20)	−78 (360)[b]	99 (77)[c]	87:13

[a] Conversion and ratio were determined by ^{1}H NMR analysis of the crude reaction mixture.
[b] Quenched with methanol instead of water.
[c] Isolated yield of pure product for a 10 mmol scale reaction.
[d] HDA:diisopropylamine.

mixture was quenched after 5 min with methanol (entry 8), methanol-*d* or DCl in D_2O, the starting material was recovered practically unchanged. These results show that the intense color developed does not prove the formation of a great quantity of metallated product. When the contact of the reagents was maintained at a higher temperature, the major product, (*Z*)-*N*-(prop-1-enyl)benzamide **3a**, was obtained in good yields (entries 9–11). Quenching the reaction mixture at 0°C with methanol-*d* provided essentially the (*Z*)-*N*-(3-deutero-prop-1-enyl) derivative, as shown by analysis of the ^{1}H NMR spectrum of the crude product.

These results indicate that compound **3a** was obtained from the more stable intermediate. Therefore, compound **2a** should be the result of a kinetically controlled isomerization reaction.

When the reaction was performed with LDA at −78°C, the initially predominant **2-Li** was trapped by diiso-



Scheme 2.

Table 2. Isomerization of *p*-substituted *N*-allylbenzamides **1b–e**

R (*para* substituent)	Conditions[a]	Time (min)	Conversion (%)[b]	*E*/*Z* ratio[b]
1b CH_3	A	240	92	85:15
	B	90	87	5:95
1c $CH(OMe)_2$	A	300	97	83:17
	B	90	30[c]	50:50
1d $C(OMe)_2CH_3$	A	300	98	82:18
	B	90	61	11:89
1e $C(OMe)_2Ph$	A	180	98	78:22
	B	90	84	0:100

[a] A: LDA, THF–diisopropylamine (20 equiv.), −78°C; B: *n*-BuLi, THF, −78 to 0°C, then MeOH.
[b] Conversion and ratio were determined by ^{1}H NMR analysis of the crude mixture.
[c] Partial decomposition.

propylamine to provide the (*E*)-enamide **2a** after hydrolysis (Scheme 2). At higher temperatures, an equilibrium was reached; the intermediate **3-Li** becomes predominant and finally gave (*Z*)-enamide **3a** after work-up. Semi-empirical calculations, using the PM3 method,[8,9] indicated that the more stable dilithiated species was the (*Z*)-isomer **3-Li**, as a result of an internal chelation involving the lithium atom and the oxygen and/or nitrogen atoms.[10,11] With *n*-butyllithium, because there was no reprotonating agent present, the more stable lithiated intermediate **3-Li** was favored.

Assuming that acceleration of trapping of dithiated intermediate **2-Li** enhanced the yield of isomer **2a**, treatment with LDA was carried out at −78°C in the presence of 20 equiv. of diisopropylamine and there was a small increase of the yield of (*E*)-enamine **2a** of about 10% (entries 12–14).

Finally, the results obtained with a series of *para*-substituted *N*-allylbenzamides are reported in Table 2. In summary, when the reaction proceeds under kinetic control, with LDA at −78°C, the corresponding (*E*)-*N*-(prop-1-enyl)benzamides **2b–e** are the major products. With *n*-butyllithium, the mixture prepared at −78°C and allowed to warm to 0°C, provides essentially the (*Z*)-isomers **3b–e**.

Acknowledgements

The authors are grateful to the Centre Européen de Bioprospective, to the Conseil Régional de Haute Normandie and to Janssen Laboratories for financial support for M. Delamare and S. Celanire.

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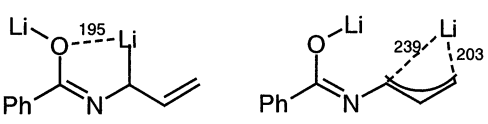
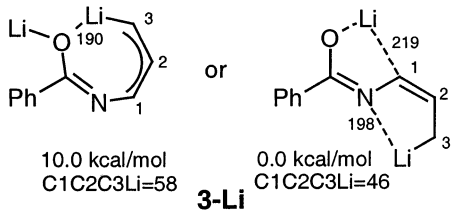
7. **Synthesis of (*E*)-*N*-(prop-1-enyl)benzamide (2a)**: To a solution of diisopropylamine (30.8 mL, 22 mmol) in tetrahydrofuran (55 mL) under nitrogen at −78°C was added *n*-butyllithium (8.8 mL, 22 mmol) 2.5 M in hexanes. The solution was stirred for 15 min at 0°C, cooled to −78°C and then treated with a solution of *N*-allylbenzamide (1.61 g, 10 mmol) in tetrahydrofuran (15 mL). The solution was stirred 6 h at −78°C, warmed to 0°C and treated with methanol (1 mL), ether (30 mL) and an aqueous solution of ammonium chloride. The organic solution was washed with aqueous ammonium chloride (4×25 mL) and brine (2×25 mL). The extract was dried over $MgSO_4$ and concentrated in vacuo. Column chromatography on silica gel using 20% EtOAc in petroleum ether afforded 1.237 g (77%) of **2a**: R_f 0.37 (EtOAc/petroleum ether 1:3); FTIR: 3296, 1640, 1529, 1316, 954, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.29 (s, 1H), 7.79 (dd, $J=2.2$ and 8.3 Hz, 2H), 7.49–7.44 (m, 1H), 7.39–7.34 (m, 2H), 6.92 (ddq, $J=1.6$, 10.3 and 14.1 Hz, 1H), 5.37 (dq, $J=6.7$ and 14.1 Hz, 1H), 1.69 (dd, $J=1.6$ and 6.7 Hz) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.9, 134.2, 132.1, 128.9, 127.5, 124.1, 109.6, 15.4 ppm.
Synthesis of (*Z*)-*N*-(prop-1-enyl)benzamide (3a): To a solution of *N*-allylbenzamide (1.61 g, 10 mmol) in tetrahydrofuran (55 mL) under nitrogen at −78°C was added *n*-butyllithium (8.8 mL, 22 mmol) 2.5 M in hexanes. The solution was stirred for 15 min at −78°C and then for a further 90 min at 0°C. The solution was cooled to −78°C and treated with methanol (1 mL), ether (30 mL) and an aqueous solution of ammonium chloride. The organic solution was washed with aqueous ammonium chloride (25 mL) and brine (2×25 mL). The extract was dried over $MgSO_4$ and concentrated in vacuo. Column chromatography on silica gel using 20% EtOAc in petroleum ether afforded 1.205 g (75%) of **3a**: R_f 0.44 (EtOAc/petroleum ether 1:3); FTIR: 3260, 1637, 1518, 1292, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.82–7.78 (m, 2H), 7.73 (m, 1H), 7.54–7.40 (m, 3H), 7.92 (ddq, $J=1.7$, 8.8 and 10.7 Hz, 1H), 4.93 (dq, $J=8.8$ and 7.0 Hz, 1H), 1.70 (dd, $J=1.7$ and 7.0) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.9, 134.4, 132.3, 129.1, 127.5, 122.7, 106.7, 11.4 ppm.
8. Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 221. Mopac 6.0: *QCPE 455*; Indiana University: IN, USA, 1990.
9. PM3 lithium parameters: Anders, E.; Koch, R.; Freunscht, P. *J. Comput. Chem.* **1993**, *14*, 1301.
10. The relative energies and selected geometric parameters (distances [pm], torsional angles [°]) are shown as follows.





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