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# Synthesis and properties of phenylogous amides

Ryu Yamasaki [a,*,†], Hirokazu Ikeda [a], Hyuma Masu [b,c], Isao Azumaya [b], Shinichi Saito [a,*]

[a] Department of Chemistry, Faculty of Science, Tokyo University of Science, Shinjuku, Tokyo 162-8601, Japan
[b] Faculty of Pharmaceutical Sciences at Kagawa Campus, Tokushima Bunri University, Shido, Sanuki, Kagawa 769-2193, Japan
[c] Chemical Analysis Center, Chiba University, Inage, Chiba 263-8522, Japan

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ABSTRACT

Vinylogy is a widely accepted principle involving the transfer of electronic chemical character through a double bond, and many reactions have been developed by applying this concept. In contrast, phenylogy, which involves the connection of two substituents through a benzene ring, is rarely recognized as a related idea. In this article, we present synthesis and physical properties, including their structure and reactivity of phenylogous amides. This amide mimetic unit is relatively stable and easily prepared by the Hartwig–Buchwald amination reaction. The effect of the resonance was examined by means of crystallography, reactivity and UV–vis spectroscopy.



## 1. Introduction

The amide bond is a vital component of biomolecules, such as proteins and peptides, and its formation has been a very important topic in organic chemistry.[1] In addition, tremendous efforts have been focused of the preparation of amide bond mimetics for the construction of protein prototypes and related structures for application in drug discovery.[2]

Vinylogy is a well-known concept in organic chemistry, in which the electronic character of a functional group, such as an ester or an amide can be propagated via double-bonds.[3] As for the application of this character, many vinylogous aldol reactions have been developed.[4] Phenylogy, in which the phenyl group is used instead of the double bond, is a concept closely related to that of vinylogy,[5] with *para*- and *ortho*-substituted phenylogous amides in particular, expected to have considerable effect because of their resonance structures (Fig. 1). There have, however, been few reports concerning the systematic synthesis and evaluation of properties of the phenylogous amide unit.[6] This is partly due to the fact that an effective synthetic method for this unit was not known for a long time. The situation was recently changed, however, by the development of an amination coupling reaction pioneered by Hartwig and Buchwald.[7] The majority of recent reports concerning the synthesis of phenylogous amides used N-arylation reactions catalyzed by transition metals.[8] None of those studies, however, placed a focus on the phenylogous amide unit included in the product. Toward the future application as a peptide mimetic, the general synthesis and properties of the phenylogous amide unit, will be discussed in this paper.

## 2. Results and discussion

### 2.1. Synthesis of phenylogous amides

Our plan to pursue the phenylogous unit is shown in Table 1. *p*-Bromobenzophenone (**4a**) was reacted with aniline (**7** or **8**) to afford the desired phenylogous compound **1a** or **1b** in the presence of a catalytic amount of $Pd_2(dba)_3$, ligand (XPhos (**L1**)[9] or MePhos (**L2**)[10]) and NaO$^t$Bu as a base in toluene. When 1.25 mol % of $Pd_2(dba)_3$ and 2.5 mol % of XPhos were used for the coupling reaction between **4a** and **7**, **1a** was obtained in 85% yield (entry 1). *p*-Toluidine (**8**) was also found to be a good substrate, and **1b** was obtained in a similar yield under identical conditions (entry 2). Aryl chloride (**4b**) was also tolerated by this reaction (entry 3). The yield of the product (**2a**) dramatically decreased when *o*-bromobenzophenone (**5**) was applied as the substrate (entry 4). The yield was marginally improved, however, by the use of MePhos as the ligand instead of XPhos (entry 5) and further improvement was achieved by increasing the amount of the catalyst (entries 6 and 7). *m*-Bromobenzophenone (**6**) was also tolerated as the substrate, although the products (**3a** and **3b**) were isolated in slightly lower yields (entries 8–10).

* Corresponding authors. Tel.: +81 3 5228 8715; fax: +81 3 5261 4631; e-mail addresses: yamaryu@rs.kagu.tus.ac.jp (R. Yamasaki), ssaito@rs.kagu.tus.ac.jp (S. Saito).
† Present address: Molecular Engineering Institute, Kinki University, Iizuka, Fukuoka 820-8555, Japan.

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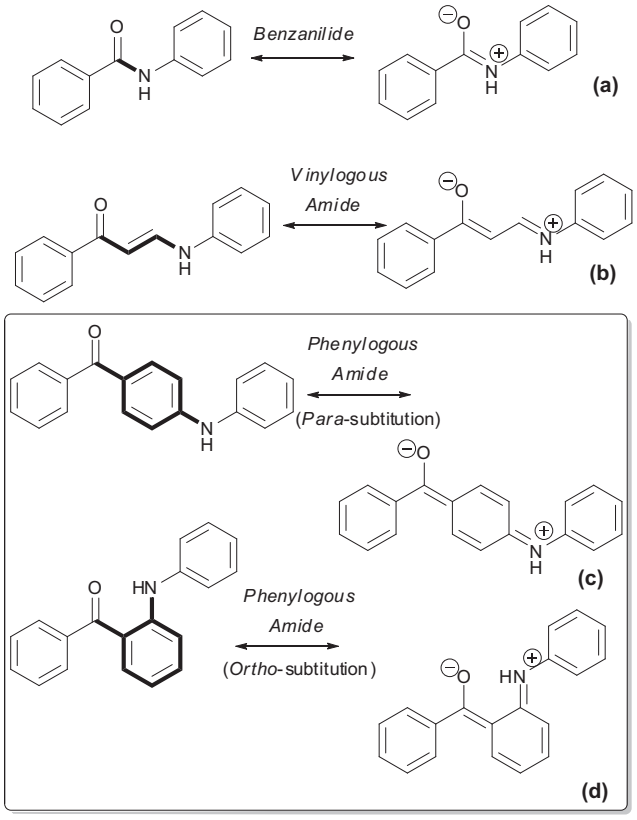



**Fig. 1.** Resonance structures of benzanilide (a), a vinylogous amide (b), and phenylogous amides (c, d).

A selective coupling reaction was achieved by the tuning of the conditions used for the coupling reactions (Fig. 2). When Xantphos[11] was used as the ligand, the reaction of aryl iodide proceeded preferentially in the presence of aryl bromide, and the corresponding product (**10**) was obtained in 71% yield. The selective coupling reaction of an aryl bromide in the presence of an aryl chloride was readily achieved when (*S*)-BINAP was used as the ligand,[12] with the coupling product (**12**) being obtained in 87% yield. This reaction was also applied to a successive one-pot coupling reaction, in which **9** was reacted sequentially with aniline and *p*-toluidine to give the double coupling product (**13**) in 61% yield.

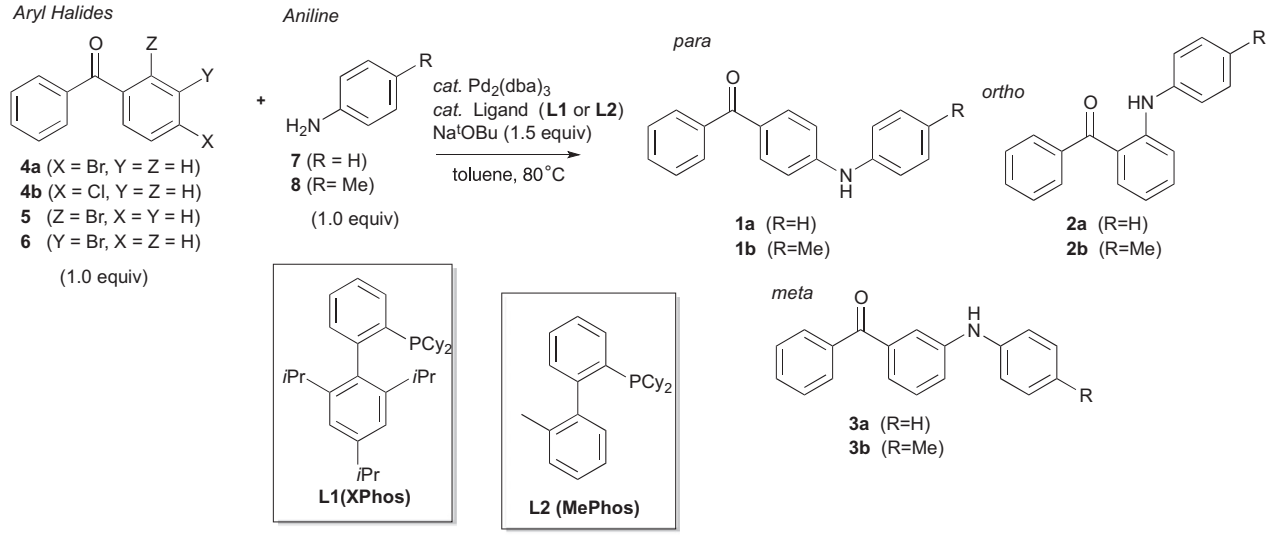
The coupling conditions used for the synthesis of the phenylogous amides were robust and applicable to the synthesis of several other derivatives (Fig. 3). For example, the introduction of a methyl group at the *ortho*-position did not interfere with the reaction, and the reaction between **14** and *o*-toluidine (**15**) proceeded smoothly (Eq. 4). The coupling of the 2-pyridine derivative (**17**) with 2-aminopyridine (**18**) was also well tolerated, affording the corresponding coupling product (**19**) in good yield (Eq. 5).

## 2.2. Crystallographic studies

To experimentally confirm the effects of resonance, the phenylogous amides and related compounds (**1a**, **2b** and **3b**) were subjected to crystallographic analysis. The results are summarized in Fig. 4.

All of the compounds analyzed formed hydrogen bonds between the carbonyl and amino groups in the crystals. The crystal structure of **1a** revealed the formation of a ladder-type hydrogen bond network. In contrast, a dimeric structure generated by hydrogen bonds was found in the crystal of **3b**. The formation of a six-

**Table 1**
Optimization of the coupling reaction




| Entry | Aryl halide | Amine | $Pd_2(dba)_3$ (mol %) | Ligand | Ligand (mol %) | Reaction time (d) | Product | Yield (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | **4a** | **7** | 1.25 | **L1** | 2.5 | 1 | **1a** | 85 |
| 2 | **4a** | **8** | 1.25 | **L1** | 2.5 | 1 | **1b** | 87 |
| 3 | **4b** | **7** | 1.25 | **L1** | 2.5 | 1 | **1a** | 78 |
| 4 | **5** | **7** | 1.25 | **L1** | 2.5 | 7 | **2a** | 26 |
| 5 | **5** | **7** | 1.25 | **L2** | 2.5 | 1 | **2a** | 38 |
| 6 | **5** | **7** | 2.5 | **L2** | 10 | 1 | **2a** | 90 |
| 7 | **5** | **8** | 2.5 | **L2** | 10 | 1 | **2b** | 89 |
| 8 | **6** | **7** | 1.25 | **L1** | 2.5 | 7 | **3a** | 69 |
| 9 | **6** | **7** | 2.5 | **L2** | 10 | 2 | **3a** | 75 |
| 10 | **6** | **8** | 1.25 | **L1** | 2.5 | 2 | **3b** | 63 |

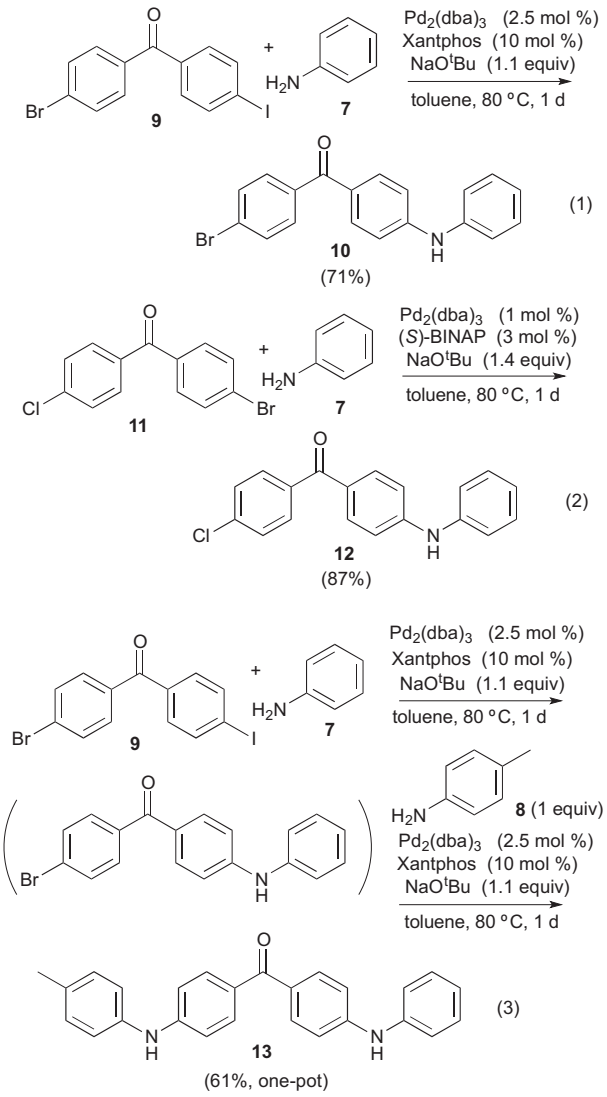



**Fig. 2.** Selective coupling and successive double coupling.

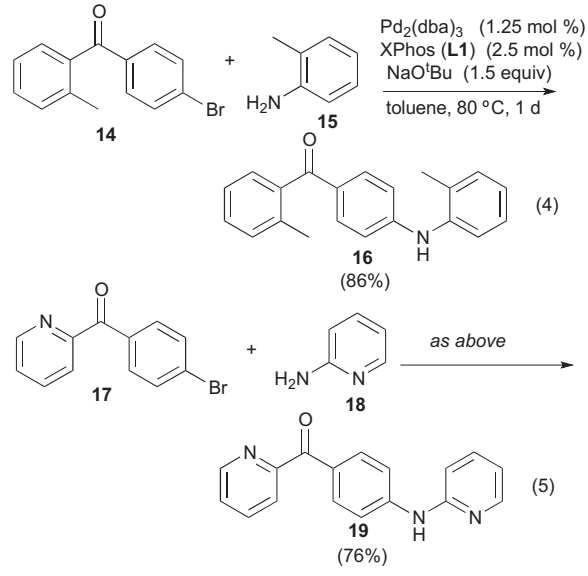



**Fig. 3.** Synthesis of various phenylogous amide derivatives.

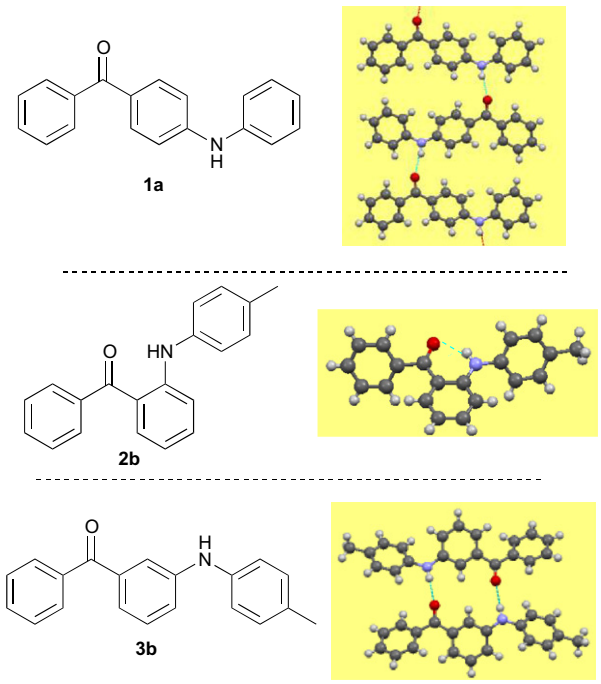



**Fig. 4.** X-ray crystal structures of **1a**, **2b**, and **3b**.

membered intramolecular hydrogen bond was observed in the crystal structure of the *ortho*-substituted phenylogous amide (**2b**). The phenyl rings of **1a**, **2b**, and **3b** were slightly twisted, presumably because of steric repulsion between the hydrogen atoms at the *ortho* positions.

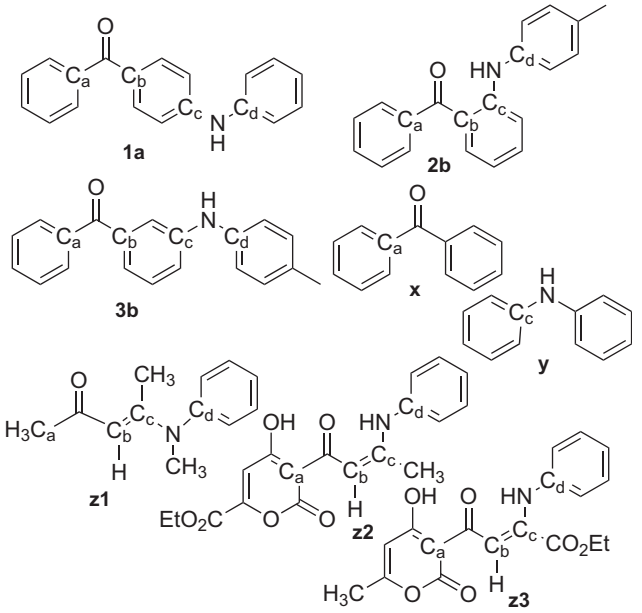
From a structural perspective, these motifs would be useful for the introduction of predictable structure, including hydrogen bond-mediated molecular assembly. We envisage that the *ortho*-substituted phenylogous unit (**2b**) could induce turn structure, and that the *para*-substituted phenylogous amide (**1a**) could form ladder-type intermolecular hydrogen bonds. Two molecules of the *meta*-substituted compounds (**3b**) formed two intermolecular hydrogen bonds, which resulted in the formation of a dimeric structure.

The effect of the resonance was also examined by comparing bond lengths (Table 2). If the resonance effect exists, the length of the C=O double bond would be longer and the C(=O)–$C_b$ and $C_c$–N bond would be shortened because of the partial double bond character. The C=O bond lengths were almost identical in compounds **1a**, **2b**, **3b**, and the reference compound, benzophenone (1.23 Å),[13] presumably because of the effect of the hydrogen bond. The bond lengths of C(=O)–$C_b$ and $C_c$–N, however, in **1a** (1.4702 Å and 1.3787 Å) and **2b** (1.474 Å and 1.369 Å) were shorter than those of the *meta* isomer **3b** (1.487–1.493 Å and 1.3910–1.3940 Å) and diphenylamine ($C_c$–N, 1.39–1.41 Å).[14] The double bond lengths ($C_b$=$C_c$) in **2b** (1.431 Å), **z1** (1.392 Å) and **z2** (1.374 Å)[15] were longer than the average lengths (1.397 Å for **2b**, 1.317 Å for **z1** and **z2**).[16] However, a more prominent resonance effect has been reported in the literature for the vinylogous amide (**z1**, **z2**, and **z3**[17]).

## 2.3. Competitive reduction

The effect of resonance on the reactivity was evaluated by conducting competitive reduction of the compounds with $NaBH_4$. A mixture of the three phenylogous amides (1 equiv each of **1a**, **2a** and **3a**), was treated with 1 equiv of $NaBH_4$ under reflux (Fig. 5). The reaction was monitored by TLC and NMR. The *para*- and *ortho*-substituted phenylogous compounds remained intact during the

**Table 2**
Bond length (Å) in crystal structures




| Compd | $C_a$–C(=O) | C=O | C(=O)–$C_b$ | $C_c$–N | N–$C_d$ |
|---|---|---|---|---|---|
| **1a** | 1.4885(17) | 1.2281(14) | 1.4702(17) | 1.3787(15) | 1.4018(16) |
| **2b** | 1.498(2) | 1.234(2) | 1.474(3) | 1.369(3) | 1.417(2) |
| **3b**-1[a] | 1.502(2) | 1.2244(18) | 1.493(2) | 1.3910(19) | 1.3995(19) |
| **3b**-2[a] | 1.500(2) | 1.2226(17) | 1.487(2) | 1.3940(18) | 1.4123(18) |
| **x**[13] | 1.48, 1.50 | 1.23 | — | — | — |
| **y**[14] | — | — | — | 1.39–1.41 | — |
| **z1**[15] | 1.495(10) | 1.210(8) | 1.452(7) | 1.455(12) | 1.425(9) |
| **z2**[15] | 1.481(2) | 1.204(2) | 1.403(2) | 1.338(2) | 1.441(2) |
| **z3**[17] | 1.453(3) | 1.209(4) | 1.438(4) | 1.342(4) | 1.427(4) |

[a] Two molecules exist in an unsymmetrical unit.

reaction, whereas the *meta*-substituted compound (**3a**) was selectively reduced by $NaBH_4$, with the resulting alcohol (**20**) being obtained in 79% yield.

The reactivity of **1a** and **2a** was then compared according to the same procedure. The results indicated that the reactivity of **2a** was greater, with **2a** being completely consumed and the corresponding alcohol (**22**) isolated in 81% yield. In contrast, most of **1a** was recovered unchanged. These results supported the existence of a resonance effect in *para*- and *ortho*-substituted phenylogous compounds. Furthermore, the *ortho*-substituted compound (**2a**) was more susceptible to the reduction than the corresponding *para*-substituted analogue (**1a**).

## 2.4. $^{13}$C NMR chemical shift of carbonyl carbon

The $^{13}$C NMR chemical shift of the carbonyl carbon indicates the electron density of the carbonyl carbon, including the effect of hydrogen bonds.[18] The peak of the carbonyl carbon was observed at 195.2 ppm for **1a**, 199.1 ppm for **2a**, and 196.7 ppm for **3a**. A similar trend was observed for the *p*-methyl substituted compounds (**1b**, **2b**, and **3b**) and aminobenzophenones[19] (Table 3). The carbonyl signal of the *para*-substituted phenylogous amides (**1a** and **1b**) shifted to a higher field compared to its *meta* analogues (**3a** and **3b**) and benzophenone (196.5 ppm). This was attributed to the effect of resonance from the anilino group at the *para* position. In contrast, the observed shift to a lower field in the *ortho*-substituted amide analogue was attributed to a strong six-membered intramoleculer hydrogen bond.

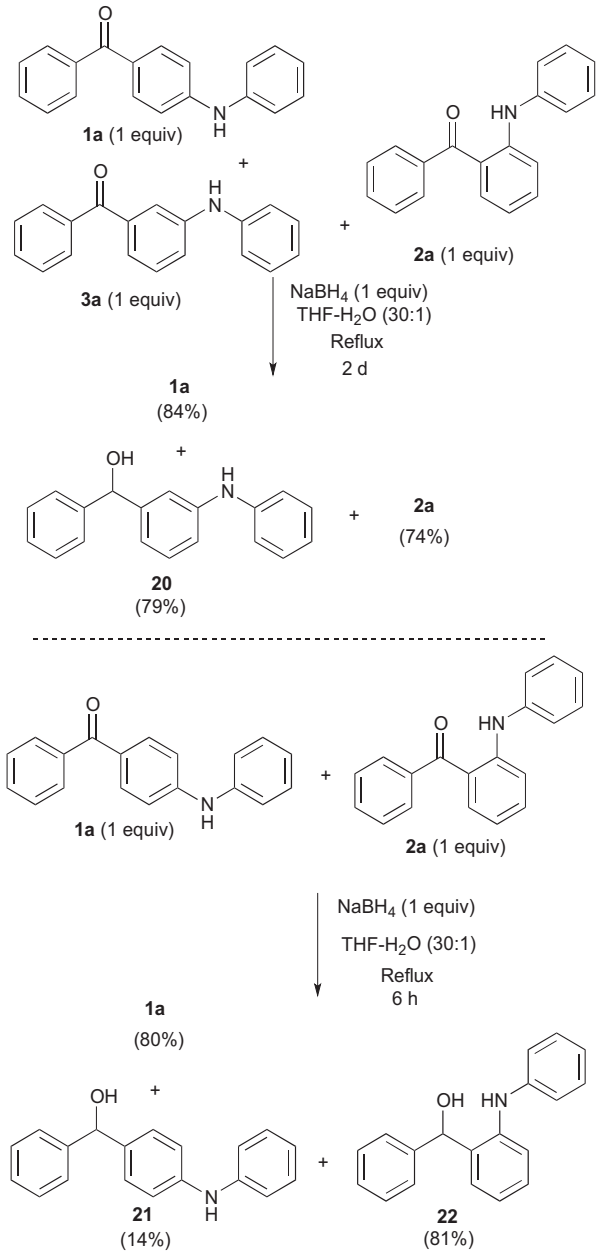



**Fig. 5.** Competitive reduction of phenylogous amides.

## 2.5. UV–vis spectroscopic study

The effect of the resonance on the structure of the compounds was further studied by UV–vis spectroscopy. The UV–vis spectra of **1a**, **2a**, and **3a** were measured in $CHCl_3$. The results are summarized in Fig. 6 and Table 4. The results were compared with the closely related studies of Casadeval and Itier,[20] who reported the UV–vis spectra of the compounds in EtOH.

The $n$–$\pi^*$ absorption band was observed at 345 nm for **1a**, and 406 nm for **2a**. No absorption was observed in the region of

**Table 3**
$^{13}$C chemical shift of carbonyl carbon in $CDCl_3$

| | *para* (ppm) | *ortho* (ppm) | *meta* (ppm) |
|---|---|---|---|
| Phenylogous (**a**) | 195.2 | 199.1 | 196.7 |
| *p*-Methyl phenylogous (**b**) | 195.1 | 199.1 | 196.7 |
| Aminobenzophenone[19] | 195.3 | 199.0 | 196.8 |

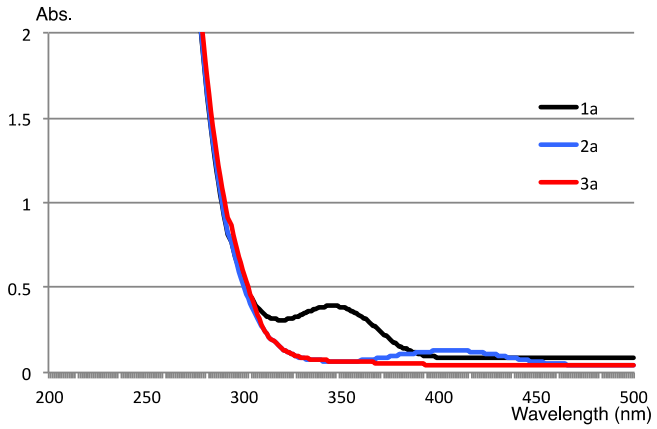



**Fig. 6.** UV–vis spectrum of **1a**–**3a** in $CHCl_3$ (1 μM) at 298 K.

**Table 4**
UV–vis spectrum of **1a**–**3a**

| Compound | **1a** | **2a** | **3a** |
|---|---|---|---|
| $\lambda_{max}$ (nm) | 345 | 406 | — |
| $\varepsilon$ | $3.93\times10^3$ | $1.30\times10^3$ | — |

300–400 nm for compound **3a**. Relative to the previous study,[20] the maximum absorption wavelength of **1a** showed a blue-shift (367 nm in 95% EtOH) in $CHCl_3$. This difference in wavelength supported the idea that the degree of resonance was higher for the *para*-substituted phenylogous amide (**1a**) than the *ortho*-substituted phenylogous amide (**2a**). This difference of degree of the resonance might result in preferred reduction of **2a** (vide supra). The higher absorption coefficient of **1a** ($\varepsilon$=3930 in $CHCl_3$, 23,400 in 95% EtOH), compared to that of **2a** ($\varepsilon$=1300 in $CHCl_3$, 6340 in 95% EtOH), was consistent with the observation made by Casadevall et al.[18]

## 3. Conclusions

In this paper, the phenylogous amides have been proposed as a potential mimetic of amide. This unit can be readily assembled using a Hartwig–Buchwald amination reaction, with a selective coupling reaction achieved through the tuning of the ligand. The properties of phenylogous amides were examined by crystallography and competitive reduction. The bond lengths of *para*- and *ortho*-substituted phenylogous amides reflected the effects of conjugation, which were dependent on the position of the substitution. Thus, the degree of conjugation was strengthened in the order *meta* isomer<*ortho* isomer<*para* isomer. The degree of resonance was comparable with those of vinylogous amides. The UV–vis study supported the existence of resonance for the *para*- and *meta*-substituted phenylogous compounds. This result was also consistent with the *meta*-selective reduction of the mixture of phenylogous amides by $NaBH_4$. The hydrogen bonds were also featured in the crystal structures. The *para*-substituted compound showed intermolecular ladder-type hydrogen bonds, whereas the *meta*-substituted compound dimerized through complementary hydrogen bonds. The *ortho*-substituted phenylogous amide showed intramolecular hydrogen bonding, which would be useful in the introduction of a β-turn structure. In the future, the use of this phenylogous unit could contribute to the construction of functional molecules, such as protein binding molecules by mimicking protein-protein interactions.

## 4. Experimental section

### 4.1. General

$^1H$ and $^{13}C$ NMR spectra were recorded on a JEOL JNM-LA500. Chemical shifts are shown in parts per million, using the residual chloroform peak ($\delta$=7.24 ppm in $^1H$ NMR) or the middle peak of the $CDCl_3$ carbon triplet ($\delta$=77.0 ppm in $^{13}C$ NMR) as internal standards.

Chemicals were used as received without further purification. Chromatography was performed on silica gel 60N. All of the compound characterization data, including the $^1H$ and $^{13}C$ NMR spectra of compounds are included in the ESI. UV–vis analyses were performed with a SHIMADZU-UV-3150PC.

### 4.2. General procedure of the coupling reaction

An oven-dried side-armed flask was charged with $Pd_2(dba)_3$ (11 mg, 0.0125 mmol), ligand (0.0250 mmol), and $NaO^tBu$ (144 mg, 1.5 mmol) and evacuated and backfilled with argon. A solid aryl halide (1 mmol) or amine (1 mmol) was added to the flask followed by the addition of $NaO^tBu$. Toluene (1.5 mL) and a liquid amine (1.0 mmol) were then added to the flask via a syringe. The resulting mixture was heated at 80 °C with stirring and the reaction was monitored by TLC. The mixture was cooled to ambient temperature, diluted with $CH_2Cl_2$ (30 mL), filtered through Celite, and concentrated in vacuo to give the crude product, which was purified by silica gel column chromatography. The compound data of **1a**[8b] and **1b**[21] were consistent with those reported elsewhere.

*4.2.1. p-Toluidino-benzophenone (**2b**).* Yellow oil, 255 mg, 89%; Purified by silica gel column chromatography (hexane/AcOEt=20:1); $^1H$ NMR (500 MHz, $CDCl_3$) 10.1 (br s, 1H), 7.74 (d, 2H, $J$=7.5 Hz), 7.61–7.57 (m, 2H), 7.53 (t, 2H, $J$=7.5 Hz), 7.36 (t, 1H, $J$=8.5 Hz), 7.32 (d, 2H, $J$=10.5 Hz), 7.26–7.21 (m, 3H), 6.71 (t, 1H, $J$=7.0 Hz), 2.41 (s, 3H); $^{13}C$ NMR (126 MHz, $CDCl_3$) 199.1, 148.8, 139.9, 137.7, 135.0, 134.2, 133.5, 131.2, 129.9, 129.3, 128.1, 122.9, 119.0, 115.9, 114.2, 20.9; IR (KBr) 4721, 4659, 4057, 3317, 3024, 2916, 2854, 1597, 1512, 1442, 1311, 1257, 1157, 1041, 926, 841, 748, 694, 517 $cm^{-1}$; Anal. Calcd for $C_{20}H_{17}NO$: C, 83.59; H, 5.96; N, 4.87. Found: C, 83.46; H, 6.02; N, 4.83. The adequate crystal for X-ray crystallography was obtained by recrystallization from $CH_2Cl_2$, and the crystal was stable only in the presence of $CH_2Cl_2$.

*4.2.2. m-Anilino-benzophenone (**3a**).* Yellow solid, 188 mg, 69%; mp 79.8–80.4 °C; Purified by silica gel column chromatography (hexane/$CH_2Cl_2$=1:1); $^1H$ NMR (500 MHz, $CDCl_3$) 7.81 (d, 2H, $J$=7.3 Hz), 7.57 (t, 1H, $J$=7.0 Hz), 7.47–7.45 (m, 3H), 7.35–7.26 (m, 5H), 7.09 (d, 2H, $J$=8.3 Hz), 6.96 (t, 1H, $J$=7.3 Hz), 5.81 (br s, 1H); $^{13}C$ NMR (126 MHz, $CDCl_3$); 196.7, 143.5, 142.2, 138.7, 137.6, 132.4, 130.0, 129.4, 129.1, 128.2, 122.4, 121.7, 120.8, 118.4, 118.3; IR (KBr) 3360, 3056, 2360, 2340, 1942, 1869, 1845, 1829, 1793, 1793, 1771, 1734, 1717, 1699, 1684, 1652, 1596, 1577, 1559, 1541, 1522, 1507, 1497, 1489, 1473, 1449, 1418, 1397, 1133, 1073, 987, 940, 877, 807, 781, 760, 715, 695, 668, 655, 641, 618 $cm^{-1}$; HRMS ($EI^+$) calcd for $C_{19}H_{15}NO$: 273.1154. Found: 273.1156.

*4.2.3. m-Toluidino-benzophenone (**3b**).* Yellow solid, 181 mg, 63%; mp 96.8–97.4 °C; $^1H$ NMR (500 MHz, $CDCl_3$) 7.80 (d, 2H, $J$=7.0 Hz), 7.56 (t, 1H, $J$=7.5 Hz), 7.45 (t, 2H, $J$=8.5 Hz), 7.39 (s, 1H), 7.31–7.19 (m, 3H), 7.08 (d, 2H, $J$=7.5 Hz), 7.01 (d, 2H, $J$=8.5 Hz), 2.29 (s, 3H), 1H (NH) was not observed; $^{13}C$ NMR (126 MHz, $CDCl_3$) 196.7, 144.3, 139.4, 138.8, 137.7, 132.4, 131.8, 130.03, 129.98, 129.1, 128.2, 121.9, 119.9, 119.5, 117.5, 20.7; IR (KBr) 3471, 3340, 3186, 3024, 2916, 2337, 1651, 1597, 1527, 1427, 1327, 1134, 987, 879, 810, 717, 640, 501 $cm^{-1}$;

Anal. Calcd for $C_{20}H_{17}NO$: C, 83.59; H, 5.96; N, 4.87. Found: C, 83.36; H, 5.87; N, 4.81.

*4.2.4. (4-Bromophenyl)-(4′-anilinophenyl)-methanone (**10**).* Yellow solid; mp 194.0–194.4 °C; $^1$H NMR (500 MHz, $CDCl_3$) 7.72 (d, 2H, *J*=9.0 Hz), 7.60 (m, 4H), 7.34 (t, 2H, *J*=7.5 Hz), 7.18 (d, 2H, *J*=7.5 Hz), 7.08 (t, 1H, *J*=7.5 Hz), 7.00 (d, 2H, *J*=8.5 Hz), 6.07 (br s, 1H); $^{13}$C NMR (126 MHz, DMSO-$d_6$) 192.5, 148.9, 140.9, 137.5, 132.3, 131.3, 131.0, 129.3, 126.2, 125.3, 122.2, 119.7, 113.8; IR (KBr) 3317, 1635, 1582, 1559, 1496, 1340, 1173, 1148, 1069, 1011, 930, 852, 761, 751, 693 cm$^{-1}$; Anal. Calcd for $C_{19}H_{14}BrNO$: C, 64.79; H, 4.01; N, 3.98. Found: C, 64.88; H, 4.10; N, 3.92.

*4.2.5. (4-Chlorophenyl)-(4′-anilinophenyl)-methanone (**12**).* Yellow solid; 184.2–184.9 °C; $^1$H NMR (500 MHz, $CDCl_3$) 7.73 (d, 2H, *J*=8.5 Hz), 7.69 (d, 2H, *J*=7.5 Hz), 7.43 (d, 2H, *J*=8.5 Hz), 7.34 (t, 2H, *J*=8.5 Hz), 7.19 (d, 2H, *J*=7.5 Hz), 7.08 (t, 1H, *J*=7.5 Hz), 7.00 (d, 2H, *J*=8.5 Hz); $^{13}$C NMR (126 MHz, $CDCl_3$) 193.8, 148.4, 140.4, 137.9, 137.0, 132.6, 131.0, 129.6, 128.4, 128.2, 123.5, 120.8, 114.3; IR (KBr) 3316, 1635, 1496, 1343, 1173, 1148, 1091, 1013, 930, 854, 763, 753, 741, 693, 674 cm$^{-1}$; Anal. Calcd for $C_{19}H_{14}ClNO$: C, 74.15; H, 4.58; N, 4.55. Found: C, 74.12; H, 4.62; N, 4.54.

*4.2.6. (2-Methyl-phenyl)-((2′-methyl)phenyl)-phenyl-methanone (**16**).* Yellow solid; mp 146.2–147.0 °C; $^1$H NMR (500 MHz, $CDCl_3$) 7.68 (d, 2H, *J*=6.7 Hz), 7.32 (t, 1H, *J*=7.7 Hz), 7.29–7.17 (m, 6H), 7.08 (t, 1H, *J*=7.4 Hz), 6.76 (d, 2H, *J*=9.0 Hz), 5.80 (s, 1H), 2.29 (s, 3H), 2.24 (s, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) 196.9, 150.0, 139.6, 138.3, 135.7, 132.5, 132.2, 131.1, 130.5, 129.3, 128.0, 127.5, 126.8, 124.98, 124.97, 123.7, 113.5, 19.6, 17.8; IR (KBr) 3341, 3262, 3019, 3020, 2760, 2604, 1934, 1635, 1578, 1552, 1523, 1424, 1379, 1336, 1314, 1295, 1277, 1182, 1150, 1112, 1039, 997, 953, 927, 843, 800, 776, 750, 732, 702, 680, 644, 631, 610, 532, 498, 445, 419, 410; Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.94; H, 6.01; N, 4.62.

*4.2.7. (2-Pyridiyl)-(2′-pyridiyl)phenyl-methanone (**19**).* Yellow solid; mp 158.9–160.1 °C; $^1$H NMR (500 MHz, $CDCl_3$) 8.70 (d, 1H, *J*=4.3 Hz), 8.27 (d, 1H, *J*=4.3 Hz), 8.11 (d, 2H, *J*=8.6 Hz), 7.98 (d, 1H, *J*=7.6 Hz), 7.87 (t, 1H, *J*=6.4 Hz), 7.57 (t, 1H, *J*=7.1 Hz), 7.45 (d, 3H, *J*=8.5 Hz), 6.98 (d, 1H, *J*=8.3 Hz), 6.84 (t, 1H, *J*=7.1 Hz), 6.80 (s, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) 192.0, 155.9, 154.3, 148.3, 148.2, 145.3, 138.0, 137.0, 133.2, 129.4, 125.8, 124.5, 117.0, 116.5, 110.3; IR (KBr) 3356, 3211, 3117, 3049, 2595, 2306, 1637, 1620, 1579, 1524, 1498, 1481, 1428, 1411, 1354, 1323, 1283, 1238, 1194, 1164, 1146, 1092, 1013, 990, 940, 899, 845, 822, 803, 750, 730, 722, 692, 673, 642, 617, 607, 571, 520, 502, 459, 403; Anal. Calcd for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26. Found: C, 74.09; H, 4.79; N, 15.10.

### 4.3. General procedure of the double coupling reaction

An oven-dried side-armed flask was charged with $Pd_2(dba)_3$ (23 mg, 0.025 mmol), Xantphos (58 mg, 0.10 mmol), NaO$^t$Bu (106 mg, 1.1 mmol) and **9**. The flask was then evacuated and backfilled with argon. Toluene (2.5 mL) and aniline (0.09 mL, 1.0 mmol) were then added to the flask via a syringe and the resulting mixture was heated with stirring to 80 °C. The reaction was monitored by TLC. Upon complete consumption of **9**, *p*-toluidine (107 mg, 1.0 mmol), $Pd_2(dba)_3$ (23 mg, 0.025 mmol), Xantphos (58 mg, 0.10 mmol), and NaO$^t$Bu (106 mg, 1.1 mmol) were added to the reaction and the flask was flushed with argon. Additional toluene (2.5 mL) was then added and the resulting mixture was heated at 80 °C with stirring until the aryl halide intermediate could no longer be detected. The mixture was cooled to ambient temperature, diluted with $CH_2Cl_2$ (30 mL), filtered through Celite, and concentrated in vacuo to give the crude product, which was purified by silica gel column chromatography.

*4.3.1. (4-Anilino)-(4′-methyl anilino)benzophenone (**13**).* Orange amorphous; $^1$H NMR (500 MHz, $CDCl_3$) 7.73 (d, 2H, *J*=8.5 Hz), 7.72 (d, 2H, *J*=8.5 Hz), 7.32 (t, 2H, *J*=8.5 Hz), 7.18 (d, 2H, *J*=7.5 Hz), 7.14 (d, 2H, *J*=7.5 Hz), 7.08 (d, 2H, *J*=7.5 Hz), 7.04 (t, 1H, *J*=7.5 Hz), 7.02 (d, 2H, *J*=8.5 Hz), 6.95 (d, 2H, *J*=7.5 Hz), 2.32 (s, 3H), 1H (NH) was not observed; $^{13}$C NMR (126 MHz, $CDCl_3$) 193.7, 148.2, 147.3, 141.0, 138.2, 133.0, 132.3, 132.2, 130.0, 129.9, 129.5, 129.2, 122.9, 121.2, 120.2, 114.6, 113.9, 20.8; IR (KBr) 3297, 2349, 1634, 1559, 1496, 1286, 1172, 1151, 930, 849, 810, 765, 748, 697, 679 cm$^{-1}$; Anal. Calcd for $C_{26}H_{22}N_2O$: C, 82.51; H, 5.86; N, 7.40. Found: C, 82.37; H, 5.93; N, 7.31.

### 4.4. Competitive reduction of a mixture of phenylogous amides

To an oven-dried side-armed flask, equipped with a magnetic stirrer and condenser, was added a solution of **1a** (0.273 g, 1 mmol), **2a** (0.273 g, 1 mmol), and **3a** (0.273 g, 1 mmol) in a mixture of THF (3.0 mL) and $H_2O$ (0.1 mL). $NaBH_4$ (0.038 g, 1 mmol) was then added in a single portion and the resulting mixture was heated to gentle reflux. Upon completion of the reaction, distilled water (3 mL) was added and the reaction mixture was stirred for an additional 5 min. The mixture was then extracted with $CH_2Cl_2$ (3×8 mL), dried over anhydrous $Na_2SO_4$, and evaporated in vacuo to give the crude product as a residue, which was purified by silica gel column chromatography to obtain **20** (216 mg, 79%), **1a** (228 mg, 84%), and **2a** (202 mg, 74%). The compound data of **21**[22] and **22**[23] were consistent with those reported elsewhere.

*4.4.1. 1-Phenyl-1-(3-anilino)-methanol (**20**).* Colorless solid; mp 109.6–110.1 °C; $^1$H NMR (500 MHz, $CDCl_3$) 7.39–7.27 (m, 6H), 7.22–7.18 (m, 3H), 7.10 (d, 1H, *J*=7.5 Hz), 6.92 (d, 2H, *J*=7.5 Hz), 6.90–6.86 (m, 2H), 6.37 (br s, 1H) 5.95 (s, 1H), 2.50 (br s, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) 143.2, 142.0, 141.8, 131.9, 129.2, 128.8, 128.7, 128.5, 127.7, 126.6, 121.0, 120.7, 118.6, 118.0, 74.6; IR (KBr) 3410, 3170, 3039, 2877, 2800, 2615, 2337, 1921, 1589, 1504, 1419, 1304, 1165, 1080, 987, 856, 748, 663, 494 cm$^{-1}$; Anal. Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.08. Found: C, 83.09; H, 6.22; N, 5.08.

### 4.5. X-ray crystallography

Single crystal X-ray diffraction data of the crystals were collected on a CCD diffractometer with graphite monochromated Mo Kα (λ=0.71073 Å) radiation. The crystal structure was solved by direct methods SHELXS-97 and refined by full-matrix least-squares SHELXL-97.[24] All non-hydrogen atoms were refined anisotropically. Some hydrogen atoms of amino groups (for **1a** and **3b**) were refined isotropically. Other hydrogen atoms were included at their calculated positions.

*4.5.1. Crystal data for **1a**.* $C_{19}H_{15}NO$, $M_r$=273.32, orthorhombic, *Pbcn*, *a*=31.221(5), *b*=12.696(2), *c*=7.2579(12) Å, *V*=2876.9(8) Å$^3$, *Z*=8, $D_{calcd}$=1.262 Mg m$^{-3}$, $2\theta_{max}$=54.12°, *T*=150 K, μ=0.078 mm$^{-1}$, 13,116 reflections measured, 3005 unique ($R_{int}$=0.0281). The final $R_1$ and $wR_2$ were 0.0386 and 0.0920 ($I>2\sigma(I)$), 0.0568 and 0.1020 (all data). CCDC 877867.

*4.5.2. Crystal data for **2b**.* $C_{20}H_{17}NO{\cdot}CH_2Cl_2$, $M_r$=372.27, orthorhombic, *Pca*2$_1$, *a*=10.401(2), *b*=21.779(4), *c*=8.1491(16) Å, *V*=1845.9(6) Å$^3$, *Z*=4, $D_{calcd}$=1.262 Mg m$^{-3}$, $2\theta_{max}$=54.36°, *T*=243 K, μ=0.360 mm$^{-1}$, 8748 reflections measured, 3703 unique ($R_{int}$=0.0173). The final $R_1$ and $wR_2$ were 0.0327 and 0.0835

($I>2\sigma(I)$), 0.0412 and 0.0884 (all data). CCDC 877868. A dichloromethane molecule is included in an asymmetric unit of the crystal.

*4.5.3. Crystal data for **3b**.* $C_{20}H_{17}NO$, $M_r$=287.35, monoclinic, $P2_1/c$, $a$=15.902(2), $b$=7.492(1), $c$=25.327(4) Å, $\beta$=94.761(2)°, $V$=3006.9(8) Å$^3$, $Z$=8, $D_{calcd}$=1.269 Mg m$^{-3}$, $2\theta_{max}$=54.32°, $T$=120 K, $\mu$=0.078 mm$^{-1}$, 14,371 reflections measured, 6124 unique ($R_{int}$=0.0264). The final $R_1$ and $wR_2$ were 0.0434 and 0.1075 ($I>2\sigma(I)$), 0.0619 and 0.1192 (all data). CCDC 877869. Two conformers exist in an asymmetric unit of the crystal.

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## Supplementary data

Electronic Supplementary data available: data of X-ray crystallography (**1a**, **2b**, **3b**) and $^1$H and $^{13}$C NMR spectra of compounds. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tet.2012.07.084.

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