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Lewis acid-catalyzed formation of Ugi four-component reaction product from Passerini three-component reaction system without an added amine

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Abstract—In the presence of a Lewis acid the phenol-Passerini three-component reaction (phenol-P-3CR) system is found to deliver a product of the phenol-Ugi four-component reaction (phenol-U-4CR). It is the first demonstration of an isocyanide as an amine equivalent in isocyanide-based multicomponent reactions (IMCRs). In general, by using Ti(O-*i*-Pr)$_4$ in MeOH both phenol-U-4CR and U-4CR products are synthesized from an aromatic aldehyde, a phenolic or carboxylic acid, and an isocyanide. Moreover, by using MeCN as the solvent, the phenol-P-3CR products can be obtained in good yields without contamination of the phenol-U-4CR products.

1. Introduction

The Passerini three-component reaction (P-3CR)[1] and the Ugi four-component reaction (U-4CR)[2] are the known isocyanide-based multicomponent reactions (IMCRs) useful for generation of molecular diversity.[3,4] In P-3CR (Eq. 1 in Chart 1) an oxo compound **1**, an isocyanide **2**, and a carboxylic acid **3** are coupled to produce an α-acyloxy carboxamide **6** while in U-4CR (Eq. 3 in Chart 1) an α-amido carboxamide **8** is formed from the reaction of an isocyanide **2**, a carboxylic acid **3**, and an imine, which is normally formed in situ from an oxo compound **1** and an amine **5**. When the carboxylic acid **3** is replaced by an electron-deficient phenolic acid **4** a Smiles rearrangement[5] is proposed as the irreversible step in the phenol-Passerini three-component reaction (phenol-P-3CR)[6] and the phenol-Ugi four-component reaction (phenol-U-4CR)[7] as shown in Eqs. 2 and 4 of Chart 1. Lewis acid catalysis, although it is not required for majority of the reported IMCRs, has been demonstrated for both P-3CR and U-4CR.[8–10] Moreover, under Lewis acid catalysis, incorporation of two isocyanide molecules into the end product (double insertion) has been observed, providing many variants of the Passerini-type reaction. These include formation of (a) 2,3-bis(alkylimino)oxetane from the reaction of **2** with acetone at −78 °C;[11] (b) 2,3-diiminotetrahydrofurans and α-arylamino arylimino-γ-butenolides from the reactions of **2** with epoxides;[12] and (c) 2,3-bis(arylimino)pyrane derivatives, unsaturated iminolactones, and 6,7-diaminobenzo[*b*]furans from the reactions of **2** with enones.[13a–d] Lewis acid-catalyzed reaction of ketones with 2 equiv of **2** was reported to afford β,γ-unsaturated α-oxocarboxamides whose α-carbon originates from **2**.[14] Monoaddition of isocyanides with ketones, epoxides, cyclic ketals, and an aziridine mediated by a Lewis acid has been disclosed, yielding various heterocycles[15a–c] and homo U-4CR products.[15d] Insertion of isocyanides into aromatic C–H was promoted by Lewis acids such as $AlCl_3$ to furnish aryl imines.[13e] Formation of byproducts was also noted for Lewis acid-catalyzed P-3CR but the detail was not examined.[8g] We report here on Lewis acid-catalyzed formation of U-4CR and phenol-U-4CR products from an aromatic aldehyde, a carboxylic or phenolic acid, and an isocyanide *in the absence of an added amine*. It offers the first demonstration of an isocyanide as an amine equivalent in IMCRs. We also report on high-yielding phenol-P-3CR in MeCN with 10 mol % *i*-Pr$_2$NEt without contamination of the phenol-U-4CR product.

2. Results and discussion

In connection with our work on synthesis of 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines from 2-aminophenols,[16] we were interested in the phenol-U-4CR reported by El Kaïm and Grimaud in 2005.[7a] During our study on the U-4CR of nitrophenols, aromatic aldehydes, glycine methyl ester hydrochloride, and isocyanides we discovered that a phenol-P-3CR took place without incorporation of the amine into the products.[17] Moreover, from the reaction of **1a**, **2a**, and **4a** (**1a**/**2a**/**4a**=1.3:1.5:1.0) carried out in MeOH at 60 °C

Keywords: Lewis acid; Phenols; P-3CR; Smiles rearrangement; U-4CR.
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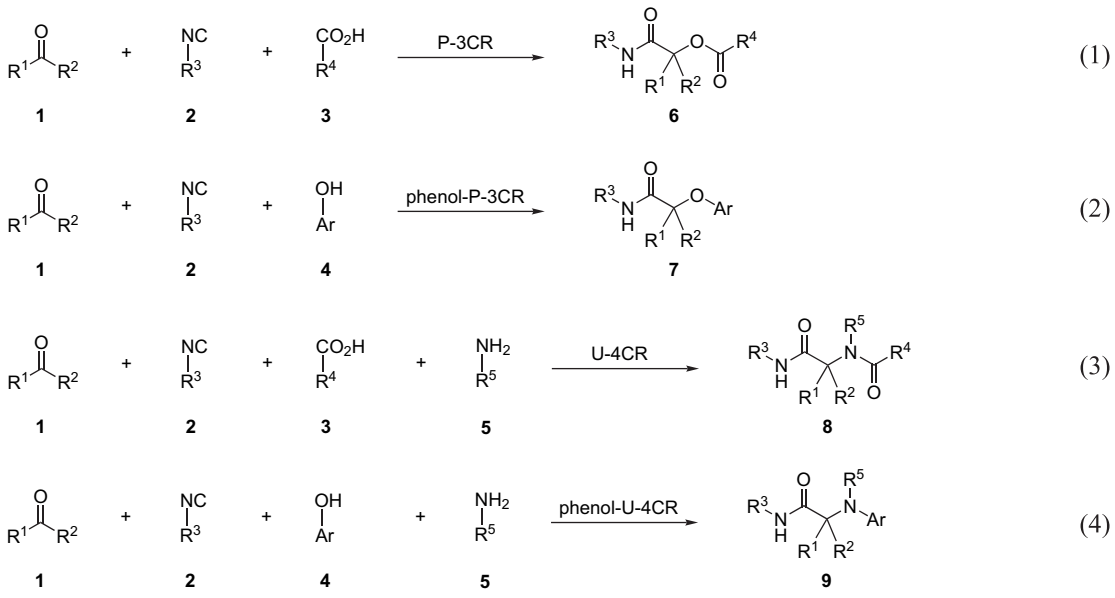
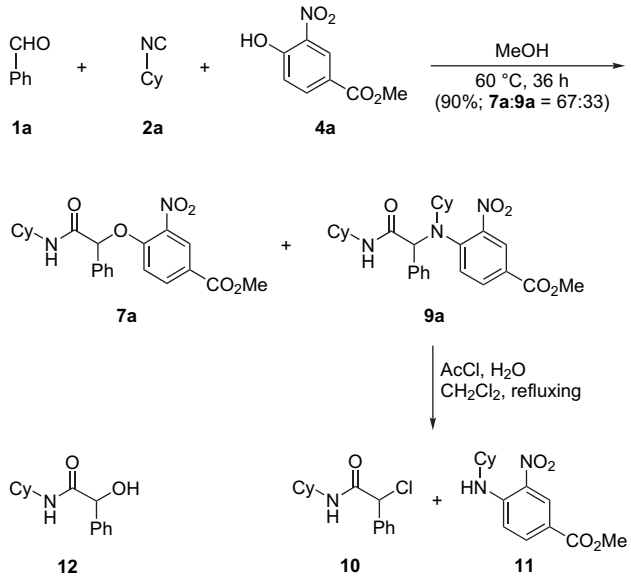


Chart 1. General description of IMCRs. P-3CR and U-4CR involve a Mumm-type rearrangement and phenol-P-3CR and phenol-U-4CR involve a Smiles rearrangement as the irreversible step, respectively.

(Scheme 1 and Fig. 1a) we obtained an inseparable mixture of the phenol-P-3CR product **7a** with a minor byproduct **9a**. The ratio of **7a/9a** is 67:33 and the combined yield is 90%. It was proved that the minor byproduct was generally produced, although to a different extent, for the reactions of aromatic aldehydes without an electron-withdrawing group such as benzaldehyde **1a**, 4-methoxybenzaldehyde, and 2-furaldehyde. Fortunately, upon treating the mixture of **7a** and **9a** with AcCl–H_2O in refluxing CH_2Cl_2, compound **9a** could be selectively decomposed, providing the pure product **7a** in 54% isolated yield (Fig. 1b). Compound **7a** was also obtained from the same reaction of **1a**, **2a**, and **4a** performed in MeCN (vide infra). As shown in Figure 1a and c, compound **9a** has a characteristic proton signal at 2.85 ppm (t, J=12.0 Hz). Because pure **9a** was not available at the time, its structure and the acid-promoted decomposition products **10** and **11** (Scheme 1) could not be firmly determined.



Scheme 1. Phenol-Passerini-3CR reaction carried out in MeOH.

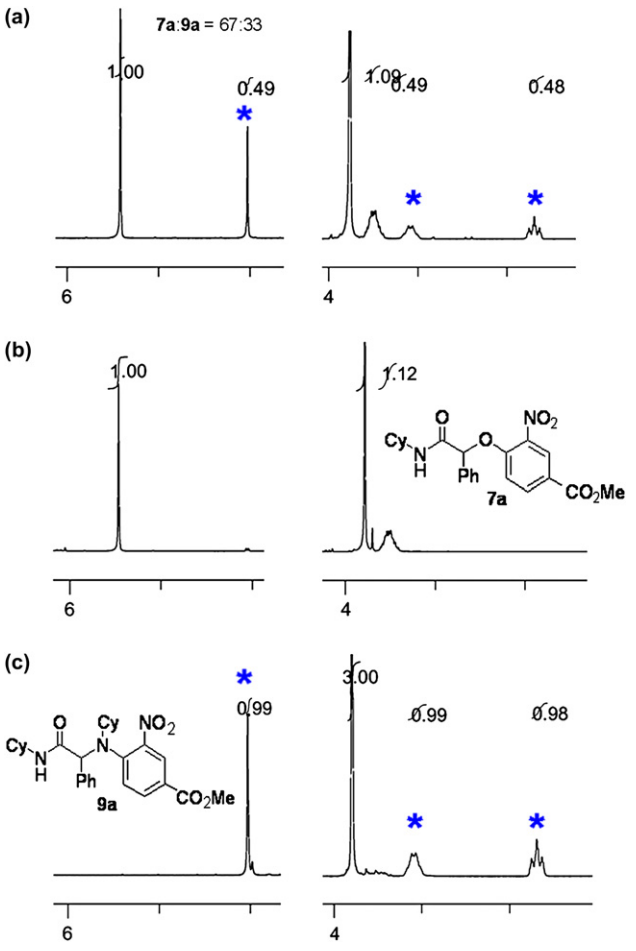
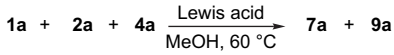


Figure 1. Partial ^{1}H NMR charts of (a) a 67:33 inseparable mixture of **7a** and **9a**; (b) pure **7a**; and (c) pure **9a**.

Table 1. Effect of Lewis acid-catalysis on phenol-U-4CR[a]



Entry	Lewis acid	t (h)	Conversion[b] (%)	**7a/9a**[c]
1	None[d]	36	100	67:33
2	None	36	100	53:47
3	$ZnBr_2$	72	88	36:64
4	$Mg(ClO_4)_2$	36	65	32:68
5	AgOTf	72	100	51:49
6	$Zn(OTf)_2$	72	47	21:79
7	$Cu(OTf)_2$	72	49	21:79
8	$Sn(OTf)_2$	72	28	15:85
9	$Sm(OTf)_3$	24	37	12:88
10	$Yb(OTf)_3$	72	30[e]	0:100
11	Ti(O-*i*-Pr)$_4$	72	46[e]	0:100
12	Ti(O-*i*-Pr)$_4$[f]	72	23[e]	0:100
13	Ti(O-*i*-Pr)$_4$[g]	24	77[e]	0:100[h]
14	Ti(O-*i*-Pr)$_4$[g]	40[i]	70[e]	0:100
15	Ti(O-*i*-Pr)$_4$[g,j]	48[i]	55	77:23
16	Ti(O-*i*-Pr)$_4$[g,k]	48[i]	58[e]	0:100

[a] All reactions were carried out in the presence of 20 mol % of Lewis acid unless otherwise stated. **1a/2a/4a**=1.3:3.0:1.0.
[b] Estimated for **4a**.
[c] Determined by ^{1}H NMR analysis.
[d] Data taken from Scheme 1. **1a/2a/4a**=1.3:1.5:1.0.
[e] Isolated yield of pure **9a**.
[f] Ti(O-*i*-Pr)$_4$ of 50 mol % was used.
[g] Ti(O-*i*-Pr)$_4$ of 5 mol % was used.
[h] Compound **12** (Scheme 1) was isolated in 10% yield.
[i] Carried out at room temperature.
[j] No solvent used.
[k] Two equivalents of MeOH used.

In searching for conditions for selective formation of **9a** we systematically examined Lewis acid catalysis for the reaction of **1a**, **2a**, and **4a**, and the results are summarized in Table 1. By using 3 equiv of cyclohexyl isocyanide **2a**, the ratio of **7a/9a** changed from 67:33 to 53:47 (entry 2 vs entry 1). $ZnBr_2$ and $Mg(ClO_4)_2$ were found to promote the formation of **9a** (entries 3 and 4). By using a series of metal triflates, the ratio of **7a/9a** increases from 51:49 to 0:100 in the order of $Ag^+<Zn^{2+}<Cu^{2+}<Sn^{2+}<Sm^{3+}<Yb^{3+}$ (entries 5–10, Table 1). However, the product **9a** was isolated only in 30% yield after 72 h at 60 °C under $Yb(OTf)_3$ catalysis. When 20 mol % Ti(O-*i*-Pr)$_4$ was used the yield of **9a** was improved to 46% (entry 11). Further increase of the Lewis acid to 50 mol %, the yield of **9a** decreased to 23% (entry 12). Finally, we were pleased to find that **9a** could be prepared in 77% yield in a pure form using 5 mol % Ti(O-*i*-Pr)$_4$ at 60 °C for 24 h (entry 13 and Fig. 1c). Moreover, the same reaction took place at room temperature for 40 h, furnishing **9a** in 70% yield (entry 14). We observed a significant solvent effect on the Lewis acid-catalyzed reaction. In the absence of a solvent, the reaction became sluggish to produce a 77:23 mixture of **7a** and **9a** (Table 1, entry 15 vs entry 14). When 2 equiv of MeOH was added, the reaction only afforded **9a** in a slightly lower yield of 58% (Table 1, entry 16 vs entry 14). The solvent effect clearly supports involvement of the solvent molecules in the formation of the phenol-U-4CR product **9a** (vide infra).

With pure **9a** in hand, we finally characterized its structure with reference to a related compound **9b**, whose structure was established by X-ray crystal structural analysis as shown in Figure 2.[18] Compound **9b** was prepared from the Lewis acid-catalyzed reaction of benzyl isocyanide as shown in entry 2 of Table 2. From pure **9a**, compounds **10** and **11** were obtained in 77% and 86% yields after the acidic decomposition (Scheme 1). It should be mentioned that a minor product **12** (10%) was obtained from the Lewis acid-catalyzed reaction of **1a**, **2a**, and **4a** but it did not formed during the acidic decomposition of **9a**. The results imply that chloride anion preferentially attacks at the protonated **9a**, instead of water, to form the product **10**.

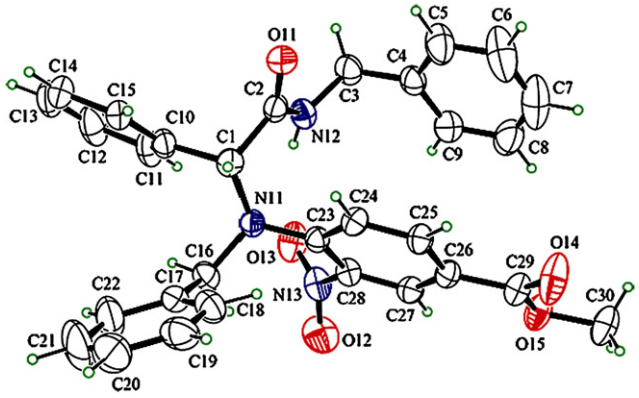
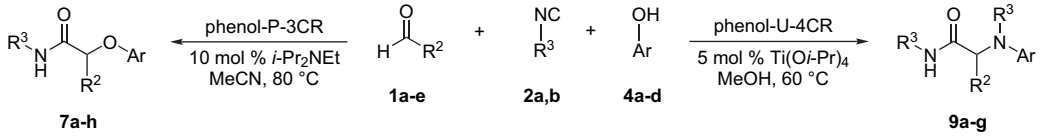
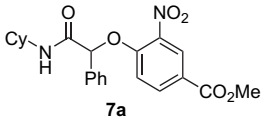
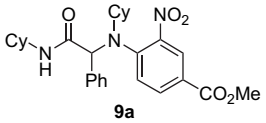
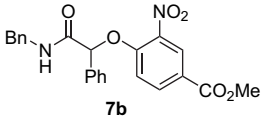
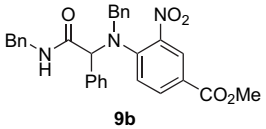
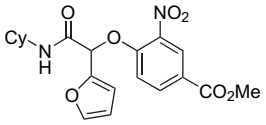
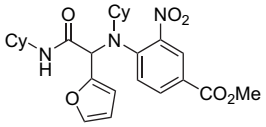
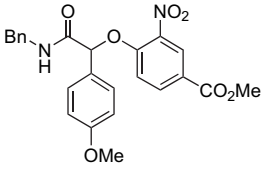
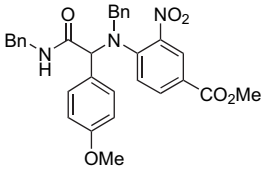
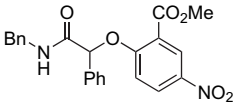
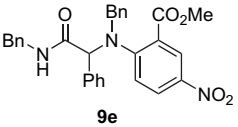
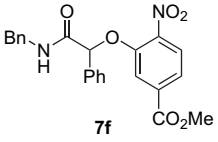
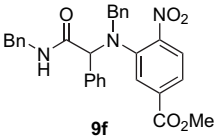
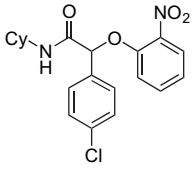
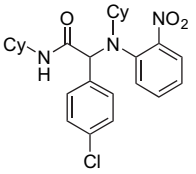
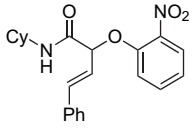


Figure 2. X-ray crystal structure of **9b**.

With the above established Ti(O-*i*-Pr)$_4$-catalyzed conditions, we selectively screened formation of the phenol-U-4CR products **9** (Chart 1, Eq. 4; R^1=H and R^5=R^3; **5** is replaced by **2**) by using four aldehydes, four phenols, and two isocyanides in MeOH at 60 °C in the presence of 5 mol % Ti(O-*i*-Pr)$_4$ (Table 2). The products **9a–g** were obtained in 43–77% isolated yields without contamination of the phenol-P-3CR products **7a–f**. However, minor products structurally similar to **12** were detected in these reactions. In El Kaïm and Grimaud's work, 2-furaldehyde fails to form phenol-U-4CR product with 4-chlorobenzylamine in MeOH at 60 °C.[6b] Under our Lewis acid-catalyzed conditions, the furan-containing compound **9c** was produced in 64% yield even at room temperature (Table 2, entry 3). Cinnamaldehyde did not form either phenol-U-4CR product nor phenol-P-3CR product in MeOH.[6b] We discovered that by using MeCN as the solvent the cinnamaldehyde-derived phenol-P-3CR product **7h** was formed at 80 °C in the presence of 10 mol % *i*-Pr$_2$NEt (Table 2, entry 8).[19] We were pleased to find out that the reaction of **1a**, **2a**, and **4a** took place by using 10 mol % *i*-Pr$_2$NEt in MeCN at 80 °C for 20 h to furnish **7a** as the sole product in 91% isolated yield (Table 2, entry 1). It differs from formation of the mixed products in MeOH as given in Scheme 1. The effect of MeCN on the phenol-P-3CR was confirmed for other related reactions and **7b–g** were synthesized in a pure form in 62–87% yields (Table 2, entries 2–7). Our method provides an improved synthesis of the known **7g** in 73% yield as compared to 57% yield obtained from the same reaction carried out in MeOH at 45 °C for 72 h.[6b] From the same set of aromatic aldehydes **1a–d**, isocyanides **2a**,**b**, and phenolic acids **4a–d**, the phenol-P-3CR products **7a–g** and the phenol-U-4CR products **9a–g** can be selectively synthesized by employing the polar, aprotic solvent, MeCN and catalytic *i*-Pr$_2$NEt, and by applying Ti(O-*i*-Pr)$_4$ catalysis in a protic solvent, MeOH, respectively.

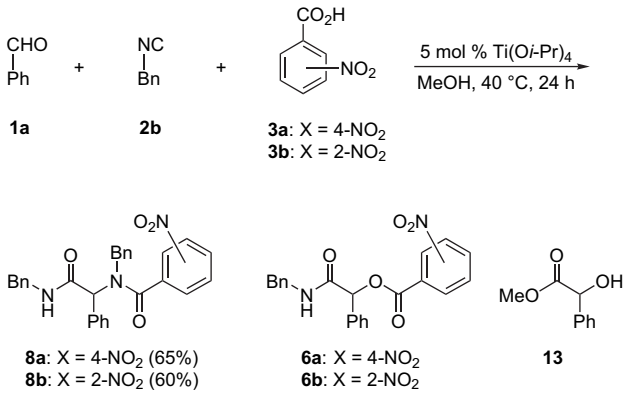
Table 2. Selective formation of phenol-P-3CR products **7a–h** and phenol-U-4CR products **9a–g** controlled by different solvents and catalytic Ti(O-*i*-Pr)$_4$



Entry	Phenol-P-3CR product **7**[a]	*t* (h)	Yield (%)	Phenol-U-4CR product **9**[b]	*t* (h)	Yield (%)
1	 **7a**	20	91	 **9a**	24	77 (plus 10% **12**)[c]
2	 **7b**	72	86	 **9b**	24	66
3	 **7c**	72	87	 **9c**	72[d]	64
4	 **7d**	72	66	 **9d**	48	51
5	 **7e**	72	62	 **9e**	48	43
6	 **7f**	72	72	 **9f**	48	45
7	 **7g**	48[e]	73	 **9g**	48	53
8	 **7h**	72	33			

[a] Carried out in MeCN at 80 °C in the presence of 10 mol % *i*-Pr$_2$NEt. **1/2/4**=1.3:1.5:1.0.
[b] Carried out in MeOH at 60 °C in the presence of 5 mol % Ti(O-*i*-Pr)$_4$. **1/2/4**=1.3:3.0:1.0.
[c] The structure of **12** is found in Scheme 1. Formation of similar compounds with **12** was observed in other entries.
[d] Carried out at room temperature in dark.
[e] Known compound, see Ref. 19.

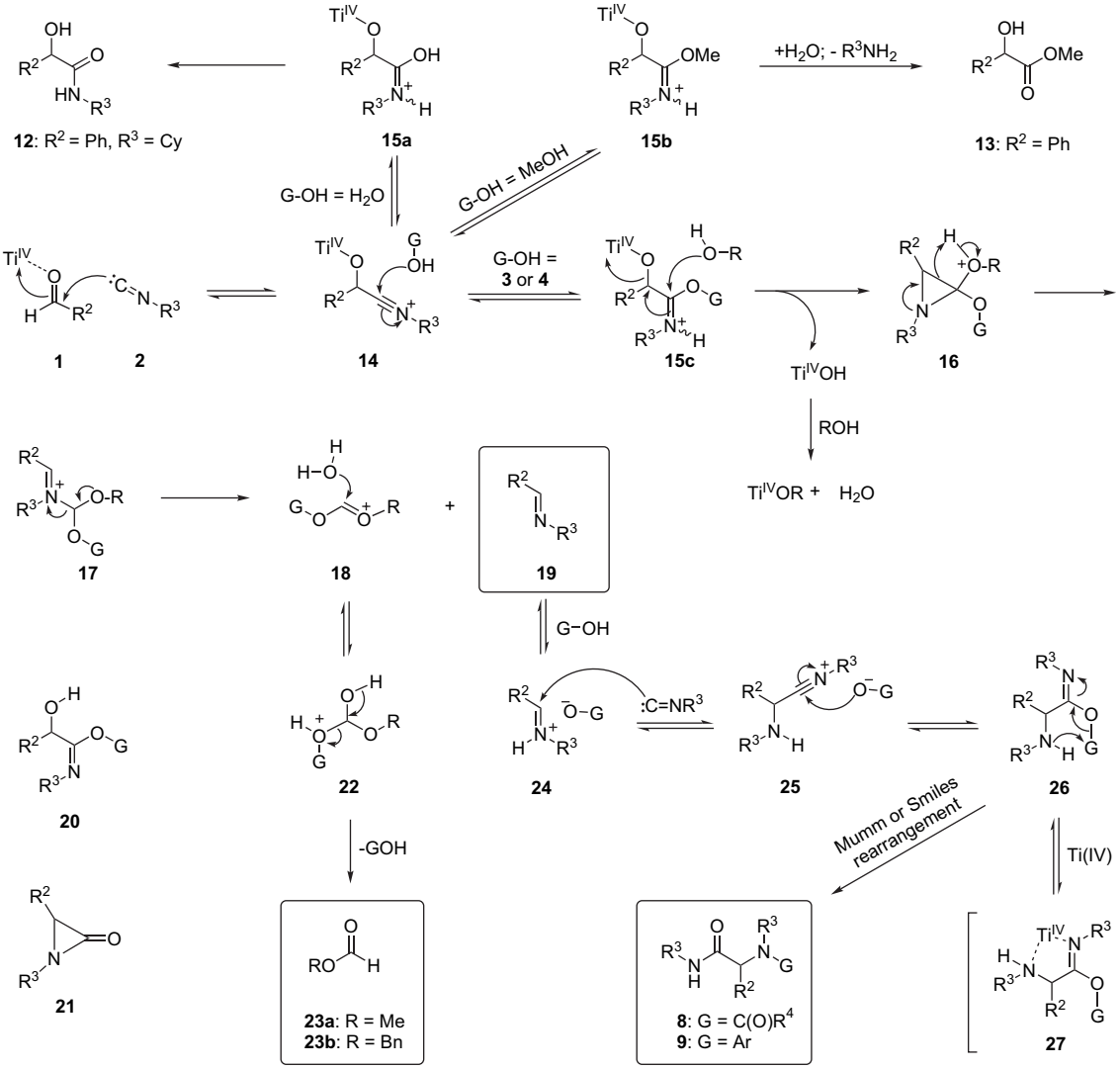
Lewis acid-catalyzed P-3CR using carboxylic acids as the acid component has been reported in the literature.[8] However, to the best of our knowledge there is no prior report on formation of the carboxylic acid-derived U-4CR products **8** (Chart 1, Eq. 3; R^1=H and R^5=R^3; **5** is replaced by **2**) from the P-3CR system without an added amine. We conducted the reaction of **1a**, **2b**, and **3a** (**1a/2b/3a**=1.3:3.0:1.0) in MeOH at 40 °C *in the presence of 5 mol % Ti(O-i-Pr)$_4$* and



Scheme 2. Lewis acid-catalyzed U-4CR without an added amine.

obtained the U-4CR product **8a** in 65% yield (Scheme 2). Similarly, **8b** was formed in 60% yield. The results clearly demonstrate that 1 equiv of isocyanide serves as the amine component required for formation of the U-4CR products. An inseparable mixture of two minor products was obtained together with **8a**. According to analysis of the ^{1}H NMR spectra, the P-3CR product **6a** and mandelic acid methyl ester **13** were likely formed. It should be emphasized that aromatic carboxylic acids such as **3a**,**b** are essential for formation of the U-4CR products **8**. Reactions using aliphatic carboxylic acids gave much more complex mixtures.

We propose a mechanism for the Lewis acid-catalyzed formation of U-4CR and phenol-U-4CR products **8** and **9** as shown in Scheme 3. In contrast to P-3CR the mechanism of U-4CR is generally accepted to involve addition of an isocyanide to an iminium species **24** and an irreversible intramolecular rearrangement within α-adduct **26**.[3a,20] In formulating our reaction mechanism, the first consideration focuses on whether an isocyanide molecule can be transformed into a primary amine or an imine species in the presence of a Lewis acid. There are several known possibilities of formation of imine derivatives via insertion of isocyanides into X–H bonds (X=O, C, P). Hydrolysis (insertion of water) of isocyanides has been used in organic synthesis[21a,b] and it is also a competing side reaction in IMCRs,[10c,20,21c,22] leading to mono *N*-substituted formamides. The latter could be converted into primary amines but only in the presence of mineral acids such as hydrochloric acid with heating at



Scheme 3. Proposed mechanism of Lewis acid-catalyzed U-4CR and phenol-U-4CR without an added amine. Ligands to Ti(IV) are omitted for clarity.

50 °C.[21a,b] In an analogous manner, insertion of carboxylic acids with isocyanides was proposed to afford either mono *N*-substituted formamides or diacyl imides.[23] Insertion of alcoholic O–H into isocyanides normally does not take place but it can be promoted by transition metals such as Ni(0)[24a] and Cu(I),[24b] affording polymeric compounds and *N*,*N*′-disubstituted formamidines, respectively. Rare-earth silylamides, $Ln[N(SiMe_3)_2]_3$ (Ln=Y, La, Sm, Yb),[25a] and actinide complexes, $[(Et_2N)_3U][BPh_4]$ and $Cp^*_2AnMe_2$ ($Cp^*=C_5Me_5$, An=U and Th),[25b] are effective for catalyzing insertion of terminal alkyne C–H with isocyanides to furnish 1-aza-1,3-enynes. $AlCl_3$-catalyzed insertion of isocyanides into electron-rich aromatic C–H is reported to produce arylimines.[13e,26] This include insertion reactions at the C3 position of indoles, and the C2 positions of pyrroles, thiophenes, and 1,3,5-trimethoxybenzene. Finally, Pd-catalyzed insertion of isocyanides into P(O)–H furnished phosphinoyl imines.[27]

Apparently the above mentioned metal-catalyzed insertion reactions of isocyanides with alcoholic O–H, C–H, and P(O)–H bonds do not apply to our Lewis acid-catalyzed U-4CR and phenol-U-4CR reactions. In order to rule out formation of a primary amine from isocyanide hydrolysis by moisture or phenols, we carried out the control experiment by treating benzyl isocyanide **2b** and the nitrophenol **4a** with 5 mol % $Ti(O\text{-}i\text{-}Pr)_4$ in MeOH at 60 °C for 24 h. The reaction mixture was analyzed directly by GC–MS and after condensation the residue was analyzed by ^1H NMR spectroscopy. The ^1H NMR spectrum showed both **2b** and **4a** being the major components along with a minor new species, which was assigned as *N*-benzylformamide (21% compared to **2b** by integrations of the benzyl protons, see page S50 of Supplementary data). GC–MS analysis gave the relative abundance according to the peak areas for **4a** (53.5%), **2b** (32.4%), *N*-benzylformamide (10.4%), and benzylamine (0.6%). Since the boiling point of benzylamine is 184–185 °C, it should not be removed during condensation of the reaction mixture. These results indicated that partial hydrolysis of **2b** occurred but the resultant *N*-benzylformamide did not further decompose into benzylamine in the presence of $Ti(O\text{-}i\text{-}Pr)_4$ in MeOH with heating. It is worthy mentioning that *N*-cyclohexylformamide was not detected by GC–MS in the reaction mixture of **1a**, **2a**, and **4a** carried out in benzyl alcohol for trapping **23b** (vide infra). The results suggest that isocyanide hydrolysis is quite slower[21c] as compared to other reactions of isocyanides.

It has been reported that addition of an isocyanide to an oxo compound in the presence of $BF_3\cdot OEt_2$ forms an imino-oxirane species, which can be converted into an α-lactam **21** (Scheme 3).[11] The latter is known to react with 'weak protic acids' (carboxylic acids and hydrofluoric acid, p*K*a>0) to produce P-3CR products while with 'strong protic acids' (sulfonic acids and hydrochloric acid, p*K*a<0) to furnish an iminium salt with decarbonylation.[28] It seems unlikely that an iminium salt can be formed via an α-lactam **21** under our phenol-U-4CR and U-4CR conditions in the absence of a strong protic acid.

As depicted in Scheme 3, we propose a new type of aziridine derivative **16** formed from the known α-adduct **15c** suggested for $Ti(OR)_4$-catalyzed P-3CR.[8g] As compared to the metal-free species **20**, the Ti(IV)-coordinated alkoxide in the complex **15c** becomes considerably inert toward a Mumm or Smiles rearrangement for the formation of P-3CR or phenol-P-3CR products. Alternatively, the oxygen at the benzylic carbon in $Ti^{IV}O\text{–}CH(R^2)$ (R^2 is an aromatic ring) is readily cleaved for cyclization toward formation of aziridine once the iminium double bond is removed by addition of a solvent molecule, ROH.[24b] Our experimental observations are consistent with formation of **16** from **15c**. Oxophilic Lewis acids such as Ti(IV), Ln(III), and Sn(II) facilitate dissociation of $Ti^{IV}O^{\delta-}\cdots C^{\delta+}H(R^2)$, giving higher ratio for the product **9a** (Table 1, entries 8–11). The developing benzylic carbocation should be stabilized by an electron-rich substituent R^2 as we observed for the aldehydes used in Table 2. The observed solvent effect (Table 1, entries 15 and 16) reinforces the notion that the alcoholic solvent, MeOH, participates in the formation of **16** from **15c**. In addition, conformational preference around the $Ti^{IV}O(R^2)HC\text{–}C(OG)=N^+HR^3$ single bond may disfavor the intramolecular rearrangement in the reactions using ortho-substituted nitrophenols and aromatic carboxylic acids. Decomposition of **16** gives the iminium ion **17**, which cleaves the oxonium fragment **18** with formation of the imine **19**. The sequence of **16**→**17**→**18**+**19** is supported by detection of benzyl formate **23b** by GC–MS analysis of the reaction mixture of **1a**, **2a**, and **4a** with benzyl alcohol used as the solvent. The water molecule involved in hydrolysis of **18** comes from cyclization of **15c**. By following the established mechanisms the U-4CR and phenol-U-4CR products **8** and **9** are obtained from **19**. We noted that high $Ti(O\text{-}i\text{-}Pr)_4$ loading decreased the yield of **9a** (Table 1, entry 12). It can be explained by formation of the Ti(IV) complex **27**, which prevents intramolecular rearrangement to the end products **8** and **9**.

We identified two side reaction products, the α-hydroxy carboxamide **12** and mandelic acid methyl ester **13**. Similar products of the type **12** were reported for the BF_3-catalyzed reaction of oxo compounds, isocyanides, and water.[14a] It should be formed by addition of water onto the nitrilium ion **14** followed by isomerization of **15a**. In a similar manner, the solvent molecule, MeOH, reacts with **14** to form the α-adduct **15b**. Hydrolysis of **15b** should produce **13**. An analogous procedure has been reported to occur under basic conditions.[10b] Moreover, **15b** can enter the same pathway described for **15c** as outlined in Scheme 3.

We attempted asymmetric U-4CR and phenol-U-4CR by employing chiral ligands-modified $Ti(OR)_4$ complexes.[29] Unfortunately, no enantioselectivity was observed.[30] The results are consistent with our proposed reaction mechanism in Scheme 3 with the imine **19** as the key reactant. Up to date there is no report on successful catalytic enantioselective U-4CR without use of chiral auxiliaries.[9]

3. Conclusion

In summary, we have established the $Ti(O\text{-}i\text{-}Pr)_4$-catalyzed formation of U-4CR and phenol-U-4CR products in MeOH from aromatic aldehydes, carboxylic or phenolic acids, and isocyanides *without added amines*. By using MeCN as the solvent, the phenol-P-3CR products are

prepared in the absence of Ti(O-*i*-Pr)$_4$. A mechanism is proposed for formation of the novel aziridine intermediate **16** from the initially formed α-adduct **15c**. It is a novel reaction pathway for IMCRs and is favored for the reactions with combination of aromatic aldehydes, aromatic carboxylic acid or phenols, and isocyanides in the presence of an oxophilic Lewis acid.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded on a 400 or 300 MHz spectrometer in $CDCl_3$ (400 or 300 MHz for ^{1}H and 100 or 75 MHz for ^{13}C, respectively) with $CHCl_3$ as the internal reference. IR spectra were taken on Nicolet Nexus FTIR 470 spectrophotometer. Mass spectra (MS) were measured by the +ESI or −ESI method on HP5989B at 70 eV. High-resolution mass spectra (HRMS) were measured by the +ESI on Bruker Apex III (7.0 Tesla) FTICRMS. Silica gel pre-coated on glass was used for thin-layer chromatography using UV light or 7% ethanolic phosphomolybdic acid and heating as the visualizing methods. Silica gel and petroleum ether (PE; bp 60–90 °C) were used for flash column chromatography. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials. Anhydrous MeOH was freshly distilled from Mg tunings. Anhydrous CH_3CN was freshly distilled from CaH_2. Other reagents were obtained commercially and used as received. Ambient temperature ranges from 10 to 30 °C.

4.2. General procedure for phenol-Passerini-3CR in MeCN with 10 mol % *i*-Pr$_2$NEt: synthesis of α-acyloxy carboxamides 7a–h

To a solution of phenol (0.20 mmol) in anhydrous MeCN (0.2 mL, 1.0 M) were added aldehyde (0.26 mmol, 1.3 equiv), *N*,*N*-diisopropylethylamine (4 μL, 0.02 mmol, 10 mol %), and isocyanide (0.30 mmol, 1.5 equiv). The resultant mixture was stirred at 80 °C under a nitrogen atmosphere for 20–72 h as specified in Table 2. The reaction mixture was concentrated under reduced pressure and the crude product was then purified by flash column chromatography (silica gel, eluted with 20% EtOAc in PE) to provide the products **7a**–**h**. The structures and yields of **7a**–**h** are listed in Table 2.

4.2.1. *N*-Cyclohexyl-2-(4′-methoxycarbonyl-2′-nitrophenoxy)-2-phenylacetamide (7a). Prepared in 91% yield (Table 2, entry 1). Compound **7a**: a pale yellow crystalline solid; mp 132–134 °C (EtOAc–hexane); R_f=0.30 (33% EtOAc in hexane); IR (KBr) 3397, 3314, 2933, 2855, 1728, 1678, 1618, 1534, 1275, 1124 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J*=1.6 Hz, 1H), 8.08 (dd, *J*=8.8, 2.4 Hz, 1H), 7.51–7.47 (m, 2H), 7.38–7.30 (m, 4H), 7.00 (d, *J*=9.2 Hz, 1H), 5.73 (s, 1H), 3.89 (s, 3H), 3.78–3.75 (m, 1H), 1.90–1.83 (m, 2H), 1.72–1.68 (m, 2H), 1.59–1.55 (m, 1H), 1.31–1.21 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 164.5, 153.3, 138.8, 135.9, 134.7, 129.2, 129.1 (×2), 128.1, 126.4 (×2), 123.8, 115.7, 81.1, 52.6, 48.1, 32.6, 32.6, 25.4, 24.5, 24.5; MS (+ESI) *m*/*z* (relative intensity) 435 (M+Na$^+$, 100). Anal. Calcd for $C_{22}H_{24}N_2O_6$: C, 64.07; H, 5.87; N, 6.79. Found: C, 64.30; H, 6.05; N, 6.58.

4.2.2. *N*-Benzyl-2-(4′-methoxycarbonyl-2′-nitrophenoxy)-2-phenylacetamide (7b). Prepared in 86% yield (Table 2, entry 2). Compound **7b**: a yellow crystalline solid; mp 149–150 °C (EtOAc–hexane); R_f=0.45 (33% EtOAc in hexane); IR (film) 3407, 3321, 2952, 1727, 1683, 1618, 1537, 1272 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J*=2.4 Hz, 1H), 8.09 (dd, *J*=8.8, 2.0 Hz, 1H), 7.72 (t, *J*=5.2 Hz, 1H), 7.54 (dd, *J*=8.4, 2.0 Hz, 2H), 7.43–7.37 (m, 3H), 7.33–7.25 (m, 5H), 7.03 (d, *J*=8.8 Hz, 1H), 5.84 (s, 1H), 4.55 and 4.46 (ABqd, *J*=15.6, 6.8 Hz, 2H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 164.4, 153.1, 138.8, 137.4, 135.8, 134.4, 129.2, 129.0 (×2), 128.6 (×2), 128.0, 127.5 (×2), 127.4, 126.3 (×2), 123.8, 115.7, 81.0, 52.5, 43.3; MS (+ESI) *m*/*z* (relative intensity) 443 (M+Na$^+$, 100), 421 (M+H$^+$, 27). Anal. Calcd for $C_{23}H_{20}N_2O_6$: C, 65.71; H, 4.79; N, 6.66. Found: C, 65.68; H, 4.78; N, 6.70.

4.2.3. *N*-Cyclohexyl-2-(4′-methoxycarbonyl-2′-nitrophenoxy)-2-(furan-2″-yl)acetamide (7c). Prepared in 87% yield (Table 2, entry 3). Compound **7c**: a white crystalline solid; mp 128–130 °C (EtOAc–hexane); R_f=0.44 (33% EtOAc in hexane); IR (film) 3397, 2933, 2855, 1728, 1686, 1617, 1533, 1271 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J*=2.4 Hz, 1H), 8.19 (dd, *J*=8.8, 1.6 Hz, 1H), 7.43 (d, *J*=8.0 Hz, 1H), 7.40 (d, *J*=1.2 Hz, 1H), 7.29 (d, *J*=8.8 Hz, 1H), 6.54 (d, *J*=3.2 Hz, 1H), 6.37–6.35 (m, 1H), 5.83 (s, 1H), 3.91 (s, 3H), 3.87–3.80 (m, 1H), 1.99–1.22 (m, 10H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.7, 164.5, 153.5, 148.4, 144.8, 139.7, 135.5, 127.1, 123.3, 116.7, 112.2, 111.3, 74.3, 53.0, 48.3, 32.5, 32.4, 25.6, 24.8, 24.7; MS (+ESI) *m*/*z* (relative intensity) 425 (M+Na$^+$, 100), 403 (M+H$^+$, 32). Anal. Calcd for $C_{20}H_{22}N_2O_7$: C, 59.70; H, 5.51; N, 6.96. Found: C, 59.70; H, 5.63; N, 6.95.

4.2.4. *N*-Benzyl-2-(4′-methoxycarbonyl-2′-nitrophenoxy)-2-(4″-methoxyphenyl)acetamide (7d). Prepared in 66% yield (Table 2, entry 4). Compound **7d**: a yellow crystalline solid; mp 139–141 °C (EtOAc–hexane); R_f=0.40 (33% EtOAc in hexane); IR (film) 3407, 3303, 2953, 1727, 1683, 1616, 1537, 1270 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J*=2.0 Hz, 1H), 8.08 (dd, *J*=8.8, 2.0 Hz, 1H), 7.68 (t, *J*=6.4 Hz, 1H), 7.45–7.40 (m, 2H), 7.32–7.23 (m, 5H), 7.02 (d, *J*=8.8 Hz, 1H), 6.92–6.87 (m, 2H), 5.76 (s, 1H), 4.53 and 4.48 (ABqd, *J*=14.8, 6.0 Hz, 2H), 3.90 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 164.4, 160.3, 153.2, 138.8, 137.5, 135.8, 128.6 (×2), 128.0, 127.8 (×2), 127.5 (×2), 127.5, 126.4, 123.7, 115.8, 114.5 (×2), 80.9, 55.2, 52.5, 43.3; MS (+ESI) *m*/*z* (relative intensity) 473 (M+Na$^+$, 100), 451 (M+H$^+$, 10). Anal. Calcd for $C_{24}H_{22}N_2O_7$: C, 63.99; H, 4.92; N, 6.22. Found: C, 64.02; H, 4.95; N, 6.25.

4.2.5. *N*-Benzyl-2-(2′-methoxycarbonyl-4′-nitrophenoxy)-2-phenylacetamide (7e). Prepared in 62% yield (Table 2, entry 5). Compound **7e**: a white crystalline solid; mp 120–122 °C (EtOAc–hexane); R_f=0.53 (33% EtOAc in

hexane); IR (film) 3350, 2953, 1722, 1682, 1524, 1346, 1258 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, J=2.0 Hz, 1H), 8.61 (t, J=5.2 Hz, 1H), 8.19 (dd, J=9.2, 2.8 Hz, 1H), 7.54–7.52 (m, 2H), 7.41–7.25 (m, 8H), 6.89 (d, J=9.6 Hz, 1H), 5.74 (s, 1H), 4.57 and 4.49 (ABqd, J=15.2, 6.4 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 163.8, 160.9, 141.2, 137.8, 134.8, 129.3, 129.1, 129.0 (×2), 128.5 (×2), 128.2, 127.8 (×2), 127.3, 126.4 (×2), 119.5, 114.9, 81.0, 52.5, 43.4; HRMS (+ESI) calcd for $C_{23}H_{20}N_2O_6Na^+$ ($M+Na^+$), 443.1214; found: 443.1199.

4.2.6. *N*-Benzyl-2-(5′-methoxycarbonyl-2′-nitrophenoxy)-2-phenylacetamide (7f). Prepared in 72% yield (Table 2, entry 6). Compound **7f**: a yellow crystalline solid; mp 134–136 °C (EtOAc–hexane); R_f=0.49 (33% EtOAc in hexane); IR (film) 3408, 3315, 2953, 1729, 1683, 1526, 1293, 1236 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J=8.4 Hz, 1H), 7.71 (dd, J=8.8, 1.2 Hz, 1H), 7.70–7.30 (m, 2H), 7.56 (d, J=6.4 Hz, 2H), 7.43–7.35 (m, 3H), 7.32–7.24 (m, 5H), 5.85 (s, 1H), 4.56 and 4.46 (ABqd, J=14.8, 6.0 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 164.5, 149.6, 141.8, 137.6, 135.6, 134.6, 129.2, 129.0 (×2), 128.6 (×2), 127.5 (×2), 127.4, 126.6 (×2), 126.3, 122.6, 116.9, 80.9, 52.9, 43.3; MS (+ESI) *m/z* (relative intensity) 443 ($M+Na^+$, 100), 421 ($M+H^+$, 18). Anal. Calcd for $C_{23}H_{20}N_2O_6$: C, 65.71; H, 4.79; N, 6.66. Found: C, 66.19; H, 4.83; N, 6.71.

4.2.7. *N*-Cyclohexyl-2-(4′-chlorophenyl)-2-(2′-nitrophenoxy)acetamide (7g).[6b] Prepared in 73% yield (Table 2, entry 7). Compound **7g**: a white crystalline solid; mp 158–159 °C (EtOAc–hexane); lit.[6b] mp 142 °C; R_f=0.45 (33% EtOAc in hexane); IR (KBr) 3391, 3268, 3081, 2931, 2854, 1655, 1525 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, J=8.0, 1.2 Hz, 1H), 7.48–7.43 (m, 3H), 7.38 (br d, J=8.0 Hz, 1H), 7.34 (d, J=8.4 Hz, 2H), 7.09 (dd, J=8.0, 8.0 Hz, 1H), 6.89 (d, J=8.4 Hz, 1H), 5.62 (s, 1H), 3.80–3.70 (m, 1H), 1.90–1.83 (m, 2H), 1.73–1.69 (m, 2H), 1.60–1.57 (m, 1H), 1.37–1.21 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 150.1, 139.1, 135.1, 134.9, 133.8, 129.1 (×2), 127.7 (×2), 126.6, 121.8, 115.7, 80.0, 48.1, 32.6 (×2), 25.4, 24.5 (×2); MS (+ESI) *m/z* (relative intensity) 413 ($M+2+Na^+$, 37), 411 ($M+Na^+$, 100). Anal. Calcd for $C_{20}H_{21}ClN_2O_4$: C, 61.78; H, 5.44; N, 7.20. Found: C, 61.78; H, 5.44; N, 7.21.

4.2.8. *N*-Cyclohexyl-2-(2′-nitrophenoxy)-4-phenyl-but-3-enamide (7h). Prepared in 33% yield (Table 2, entry 8). Compound **7h**: a pale yellow oil; R_f=0.47 (33% EtOAc in hexane); IR (film) 3388, 2932, 2854, 1676, 1606, 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, J=8.0, 1.6 Hz, 1H), 7.54 (td, J=8.0, 1.6 Hz, 1H), 7.41–7.25 (m, 6H), 7.13–7.09 (m, 2H), 6.75 (br d, J=16.4 Hz, 1H), 6.44 (dd, J=16.4, 5.6 Hz, 1H), 5.35 (dd, J=5.6, 1.6 Hz, 1H), 3.82–3.78 (m, 1H), 1.95–1.87 (m, 2H), 1.86–1.69 (m, 2H), 1.62–1.55 (m, 1H), 1.41–1.20 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 150.7, 139.2, 135.4, 135.1, 133.3, 128.6 (×2), 128.3, 126.8 (×2), 126.5, 122.8, 121.7, 115.9, 80.1, 48.2, 32.7 (×2), 25.4, 24.6 (×2); MS (+ESI) *m/z* (relative intensity) 403 ($M+Na^+$, 100); HRMS (+ESI) calcd for $C_{22}H_{24}N_2O_4Na^+$ ($M+Na^+$), 403.1620; found: 403.1610.

4.3. Representative procedure for Ti(O-*i*-Pr)$_4$-catalyzed phenol-U-4CR: synthesis of acetamide 8a,b

To a solution of *p*-nitrobenzoic acid (33.0 mg, 0.20 mmol) in anhydrous MeOH (0.2 mL, 1.0 M) were added benzaldehyde (27 μL, 0.26 mmol, 1.3 equiv), Ti(O-*i*-Pr)$_4$ (3 μL, 0.01 mmol, 5 mol %), and benzyl isocyanide (75 μL, 0.60 mmol, 3.0 equiv). The resultant mixture was stirred at 40 °C under a nitrogen atmosphere for 24 h. The reaction mixture was concentrated under reduced pressure and the crude product was then purified by flash column chromatography (silica gel, eluted with EtOAc/CH_2Cl_2/PE=1:2:2) to provide the product **8a** (65.0 mg, 65%).

4.3.1. Synthesis of *N*-benzyl-2-(*N*′-benzyl-4′-nitrobenzamido)-2-phenylacetamide (8a). Prepared in 65% yield. Compound **8a**: a white crystalline solid; mp 198–200 °C (EtOAc–hexane); R_f=0.50 (33% EtOAc in hexane); IR (KBr) 3407, 3284, 1653, 1633, 1524, 1350 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (*signal broadening is observed arising from atropisomerism*) δ 8.10 (br d, J=8.0 Hz, 2H), 7.52 (br d, J=8.8 Hz, 2H), 7.43 (br s, 1H), 7.34–7.19 (m, 9H), 7.15–7.09 (m, 3H), 6.90 (br s, 2H), 6.17 (br s, 1H), 5.80 (br s, 1H), 4.66–4.46 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) (*signal broadening is observed arising from atropisomerism*) δ 171.0, 168.8, 148.1 (×2), 142.3, 137.7, 136.7 (br), 136.5 (br), 134.1 (br), 129.9 (br, ×2), 129.0 (×2), 129.0 (×2), 128.6 (×2), 128.3 (br, ×2), 127.5 (×2), 127.4 (br), 127.1 (br), 126.6 (br), 123.5 (×2), 64.1 (br), 52.1 (br), 43.7; MS (−ESI) *m/z* (relative intensity) 478 ($M-H^+$, 100). Anal. Calcd for $C_{29}H_{25}N_3O_4$: C, 72.64; H, 5.25; N, 8.76. Found: C, 72.67; H, 5.26; N, 8.72.

4.3.2. *N*-Benzyl-2-(*N*′-benzyl-2′-nitrobenzamido)-2-phenylacetamide (8b). Prepared in 60% yield. Compound **8b**: a white crystalline solid; mp 148–150 °C (EtOAc–hexane); R_f=0.55 (50% EtOAc in hexane); IR (KBr) 3310, 1646, 1635, 1530, 1347 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (*signal broadening is observed arising from atropisomerism*) δ 8.20–8.10 (m, 1H), 7.63–7.46 (m, 5H), 7.40–7.00 (m, 14H), 6.16 (br s, 1H), 4.57 and 4.52 (ABqd, J=14.7, 6.0 Hz, 2H), 4.46 and 4.37 (ABq, J=16.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) (*signal broadening is observed arising from atropisomerism*) δ 168.4 (×2), 144.2, 137.3, 135.0, 134.0, 133.7, 132.2, 129.4 (×2), 129.2, 128.5 (×2), 128.4, 128.1, 128.0 (×2), 127.9, 127.9 (×2), 127.5, 126.9 (×2), 126.7, 123.9 (×2), 63.7, 51.9, 43.2; MS (+ESI) *m/z* (relative intensity) 502 ($M+Na^+$, 100); HRMS (+ESI) calcd for $C_{29}H_{26}N_3O_4^+$ ($M+H^+$), 480.1923; found: 480.1924.

4.4. General procedure for Ti(O-*i*-Pr)$_4$-catalyzed phenol-Ugi-4CR: synthesis of α-amido carboxamides 9a–g

To a solution of phenol (0.20 mmol) in anhydrous MeOH (0.2 mL, 1.0 M) were added aldehyde (0.26 mmol, 1.3 equiv), Ti(O-*i*-Pr)$_4$ (3 μL, 0.01 mmol, 5 mol %), and isocyanide (0.60 mmol, 3.0 equiv). The resultant mixture was stirred at 60 °C under a nitrogen atmosphere for 24–48 h. The reaction mixture was concentrated under reduced pressure and the crude product was then purified by flash column chromatography (silica gel, eluted with 20% EtOAc in PE) to provide the products **9a–g**. The structures and yields of **9a–g** are listed in Table 2.

4.4.1. *N*-Cyclohexyl-2-[*N*′-cyclohexyl-(4′-methoxycarbonyl-2′-nitrophenyl)amino]-2-phenylacetamid (9a) and *N*-cyclohexyl-2-hydroxy-2-phenylacetamide (12). Compounds **9a** and **12** were prepared in 77% and 10% yields, respectively (Table 2, entry 1). Compound **9a**: a yellow oil; R_f=0.30 (33% EtOAc in hexane); IR (film) 3361, 2933, 2855, 1731, 1673, 1532, 1290, 1249 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J=2.0 Hz, 1H), 7.94 (dd, J=8.4, 1.6 Hz, 1H), 7.66 (d, J=8.8 Hz, 1H), 7.47 (d, J=6.8 Hz, 2H), 7.23–7.17 (m, 4H), 5.01 (s, 1H), 3.90 (s, 3H), 3.56–3.53 (m, 1H), 2.85 (t, J=11.6 Hz, 1H), 1.87–0.73 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 164.6, 149.3, 143.6, 136.9, 132.1, 131.5, 128.7 (×2), 128.2 (×2), 127.9, 126.7, 125.7, 71.6, 62.9, 52.6, 47.6, 32.5, 32.3, 29.3, 29.2, 25.8, 25.8, 25.3 (×2), 24.6 (×2); HRMS (+ESI) calcd for $C_{28}H_{35}N_3O_5Na^+$ (M+Na^+), 516.2469; found: 516.2465.

Compound **12**: a colorless oil; R_f=0.30 (20% EtOAc in hexane); IR (KBr) 3342, 3264, 2934, 2853, 1642, 1060 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.32 (m, 5H), 6.00 (d, J=6.4 Hz, 1H), 4.96 (d, J=3.2 Hz, 1H), 3.75–3.73 (m, 2H), 1.84 (t, J=12.4 Hz, 2H), 1.75–1.51 (m, 3H), 1.04–1.03 (m, 2H), 1.03–1.00 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 139.7, 128.8 (×2), 128.5, 126.8 (×2), 74.0, 48.4, 32.9, 32.8, 25.4, 24.7, 24.6; HRMS (+ESI) calcd for $C_{14}H_{19}NO_2Na^+$ (M+Na^+), 256.1308; found: 256.1305.

4.4.2. *N*-Benzyl-2-[*N*′-benzyl-(4′-methoxycarbonyl-2′-nitrophenyl)amino]-2-phenylacetamide (9b). Prepared in 66% yield (Table 2, entry 2). Compound **9b**: a yellow crystalline solid; mp 117–119 °C (EtOAc–hexane); R_f=0.60 (33% EtOAc in hexane); IR (film) 3363, 1727, 1673, 1531, 1291 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J=2.0 Hz, 1H), 7.88 (dd, J=8.4, 1.6 Hz, 1H), 7.48 (d, J=6.4 Hz, 2H), 7.38–7.34 (m, 4H), 7.20–7.07 (m, 6H), 7.01 (d, J=8.8 Hz, 1H), 6.89–6.87 (m, 2H), 6.69 (d, J=7.2 Hz, 2H), 5.00 (s, 1H), 4.41 and 4.07 (ABqd, J=14.4, 7.2 Hz, 2H), 4.09 (s, 2H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 164.6, 146.1, 145.6, 137.5, 135.3, 134.1, 133.2, 129.0 (×2), 128.9 (×2), 128.7, 128.6 (×2), 128.4 (×2), 128.3 (×2), 127.9, 127.6 (×2), 127.1, 126.3, 126.2, 125.8, 70.7, 56.3, 52.5, 43.2; HRMS (+ESI) calcd for $C_{30}H_{27}N_3O_5Na^+$ (M+Na^+), 532.1843; found: 532.1817.

The structure of **9b** was confirmed by X-ray crystallographic analysis. The structural drawing is found in Figure 2.[18]

4.4.3. *N*-Cyclohexyl-2-[*N*′-cyclohexyl-(4′-methoxycarbonyl-2′-nitrophenyl)amino]-2-(furan-2″-yl)acetamide (9c). Prepared in 64% yield at room temperature for 72 h in dark (Table 2, entry 3). Compound **9c**: a yellow oil; R_f=0.30 (33% EtOAc in hexane); IR (film) 3364, 2933, 2855, 1731, 1682, 1537, 1289, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J=2.0 Hz, 1H), 7.98 (dd, J=8.4, 1.6 Hz, 1H), 7.68–7.66 (br s, 1H, –N*H*), 7.28 (d, J=8.8 Hz, 1H), 7.21 (br s, 1H), 6.33 (d, J=2.8 Hz, 1H), 6.16 (d, J=2.0 Hz, 1H), 5.08 (s, 1H), 3.89 (s, 3H), 3.75–3.60 (m, 1H), 2.78 (t, J=12.0 Hz, 1H), 1.90–0.75 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 164.6, 149.2, 149.1, 144.0, 142.4, 132.2, 130.7, 127.8, 125.5, 110.7, 110.6, 64.1, 63.7, 52.5, 48.0, 32.5, 32.5, 30.6, 29.0, 26.0, 25.7, 25.3, 25.2, 24.7 (×2); MS (+ESI) m/z (relative intensity) 506 (M+Na^+, 100); HRMS (+ESI) calcd for $C_{26}H_{33}N_3O_6Na^+$ (M+Na^+), 505.2262; found: 506.2241.

4.4.4. *N*-Benzyl-2-[*N*′-benzyl-(4′-methoxycarbonyl-2′-nitrophenyl)amino]-2-(4″-methoxyphenyl)acetamide (9d). Prepared in 51% yield (Table 2, entry 4). Compound **9d**: a yellow crystalline solid; mp 153–155 °C (EtOAc–hexane); R_f=0.50 (33% EtOAc in hexane); IR (film) 3363, 3312, 1724, 1667, 1612, 1530, 1512, 1251 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J=1.6 Hz, 1H), 7.88 (dd, J=8.4, 1.6 Hz, 1H), 7.37 (br d, J=9.2 Hz, 2H), 7.30 (t, J=6.0 Hz, 1H, –N*H*), 7.20–7.08 (m, 6H), 6.99 (d, J=8.4 Hz, 1H), 6.93–6.87 (m, 4H), 6.69 (br d, J=6.8 Hz, 2H), 4.94 (s, 1H), 4.42 and 4.11 (ABqd, J=14.4, 7.2 Hz, 2H), 4.09 (s, 2H), 3.93 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 164.7, 159.9, 146.2, 145.6, 137.6, 134.3, 133.1, 129.9 (×2), 129.0 (×2), 128.4, (×2), 128.3 (×2), 127.8, 127.6 (×2), 127.2, 127.2, 126.3, 126.2, 125.9, 114.3 (×2), 70.1, 56.2, 55.3, 52.5, 43.3; MS (+ESI) m/z (relative intensity) 562 (M+Na^+, 100), 540 (M+H^+, 24). Anal. Calcd for $C_{31}H_{29}N_3O_6$: C, 69.00; H, 5.42; N, 7.79. Found: C, 69.03; H, 5.41; N, 7.79.

4.4.5. *N*-Benzyl-2-[*N*′-benzyl-(2′-methoxycarbonyl-4′-nitrophenyl)amino]-2-phenylacetamide (9e). Prepared in 43% yield (Table 2, entry 5). Compound **9e**: a yellow crystalline solid; mp 146–148 °C (EtOAc–hexane); R_f=0.60 (33% EtOAc in hexane); IR (film) 3308, 1721, 1667, 1521, 1339, 1266 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J=2.4 Hz, 1H), 8.02 (dd, J=8.8, 2.4 Hz, 1H), 8.03–7.98 (br s, 1H, –N*H*), 7.47–7.44 (m, 2H), 7.39–7.30 (m, 3H), 7.20–7.09 (m, 6H), 7.00 (d, J=9.2 Hz, 1H), 6.95 (dd, J=8.0, 1.2 Hz, 2H), 6.68 (d, J=7.2 Hz, 2H), 5.03 (s, 1H), 4.47 and 4.09 (ABqd, J=14.4, 6.8 Hz, 2H), 416 and 4.06 (ABq, J=14.4 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 166.4, 155.0, 142.8, 137.9, 135.6, 134.8, 128.9 (×2), 128.8 (×2), 128.8 (×2), 128.6, 128.3 (×4), 127.9 (×2), 127.7, 127.4, 127.2, 126.8, 126.5, 125.0, 71.8, 57.5, 52.8, 43.3; MS (+ESI) m/z (relative intensity) 548 (M+K^+, 100), 532 (M+Na^+, 73), 510 (M+H^+, 15). Anal. Calcd for $C_{30}H_{27}N_3O_5$: C, 70.71; H, 5.34; N, 8.25. Found: C, 70.74; H, 5.33; N, 8.25.

4.4.6. *N*-Benzyl-2-[*N*′-benzyl-(5′-methoxycarbonyl-2′-nitrophenyl)amino]-2-phenylacetamide (9f). Prepared in 45% yield (Table 2, entry 6). Compound **9f**: an orange crystalline solid; mp 137–139 °C (EtOAc–hexane); R_f=0.58 (33% EtOAc in hexane); IR (film) 3368, 1729, 1667, 1529, 1282 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, J=8.4, 1.6 Hz, 1H), 7.68 (d, J=1.2 Hz, 1H), 7.54–7.50 (m, 3H), 7.46 (d, J=8.8 Hz, 1H), 7.40–7.32 (m, 3H), 7.21–7.080 (m, 6H), 6.92 (dd, J=7.6, 1.6 Hz, 2H), 6.67 (d, J=7.2 Hz, 2H), 5.00 (s, 1H), 4.43 and 4.14 (ABqd, J=14.4, 6.8 Hz, 2H), 4.06 and 4.00 (ABq, J=13.6 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 164.7, 149.8, 142.0, 137.7, 135.7, 134.1, 133.5, 129.4 (×2), 128.9 (×2), 128.7 (×2), 128.6, 128.4 (×2), 128.3 (×2), 128.1, 127.9, 127.6 (×2), 127.2, 126.5, 124.3, 71.5, 57.5, 52.7, 43.2; MS (+ESI) m/z (relative intensity) 548 (M+K^+, 100), 532 (M+Na^+, 80), 510 (M+H^+, 22). Anal. Calcd for $C_{30}H_{27}N_3O_5$: C, 70.71; H, 5.34; N, 8.25. Found: C, 70.74; H, 5.34; N, 8.25.

4.4.7. *N*-Cyclohexyl-2-[*N*′-cyclohexyl-(5′-methoxycarbonyl-2′-nitrophenyl)amino]-2-(4″-chlorophenyl)acetamide (9g). Prepared in 53% yield together with 10% of **7g** (Table 2, entry 7). Compound **9g**: a yellow crystalline solid; mp 165–167 °C (EtOAc–hexane); R_f=0.46 (33% EtOAc in hexane); IR (film) 3361, 1731, 1674, 1533, 1290 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J=2.0 Hz, 1H), 7.96 (dd, J=8.0, 1.6 Hz, 1H), 7.58 (d, J=8.8 Hz, 1H), 7.42 (d, J=8.4 Hz, 2H), 7.20 (d, J=8.4 Hz, 2H), 7.16 (d, J=8.4 Hz, 1H), 5.00 (s, 1H), 3.91 (s, 3H), 3.54–3.52 (m, 1H), 2.84–2.78 (m, 1H), 1.83–0.72 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 164.5, 149.4, 143.2, 135.6, 134.1, 132.3, 131.5, 129.5 (×2), 129.0 (×2), 128.2, 125.8, 71.0, 62.9, 52.7, 47.7, 32.5, 32.4, 29.3, 29.2, 25.8, 25.8, 25.3, 25.3, 24.6 (×2); MS (+ESI) *m*/*z* (relative intensity) 552 ($M+2+Na^+$, 29), 550 ($M+Na^+$, 100), 530 ($M+2+H^+$, 10), 528 ($M+H^+$, 21). Anal. Calcd for $C_{28}H_{34}ClN_3O_5$: C, 63.69; H, 6.49; N, 7.96. Found: C, 63.69; H, 6.50; N, 7.97.

4.5. Acidic hydrolysis of amide 9a: formation of *N*-cyclohexyl-2-chloro-2-phenylacetamide (10) and *N*-cyclohexyl-4-methoxycarbonyl-2-nitroaniline (11)

To a mixture of AcCl (0.28 mL, 4.00 mmol, 20 equiv) and H_2O (72 μL, 4.00 mmol, 20 equiv) was added a solution of compound **9a** (99.0 mg, 0.20 mmol) in CH_2Cl_2 (2.0 mL). The resulting mixture was then refluxed for 12 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (silica gel, eluted with 10% EtOAc in PE) to give compound **10** (39.0 mg, 77%) and compound **11** (48.0 mg, 86%).

4.5.1. *N*-Cyclohexyl-2-chloro-2-phenylacetamide (10). Obtained in 77% yield from **9a** as a white crystalline solid; mp 124–125 °C (CH_2Cl_2–hexane); R_f=0.35 (20% EtOAc in hexane); IR (KBr) 3424, 3305, 2937, 2854, 1656, 1641, 1537 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.33 (m, 5H), 6.66 (br s, 1H), 5.34 (s, 1H), 3.83–3.75 (m, 1H), 2.00–1.90 (m, 2H), 1.74–1.70 (m, 2H), 1.64–1.59 (m, 1H), 1.47–1.31 (m, 2H), 1.28–1.15 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 137.3, 128.9, 128.8 (×2), 127.7 (×2), 61.7, 48.8, 32.8, 32.6, 25.4, 24.6 (×2); MS (+ESI) *m*/*z* (relative intensity) 276 ($M+2+Na^+$, 29), 274 ($M+Na^+$, 100), 252 ($M+H^+$, 18). Anal. Calcd for $C_{14}H_{18}ClNO$: C, 66.79; H, 7.21; N, 5.56. Found: C, 66.77; H, 7.17; N, 5.51.

4.5.2. *N*-Cyclohexyl-4-methoxycarbonyl-2-nitroaniline (11). Obtained in 86% yield from **9a** as a yellow crystalline solid; mp 82–84 °C (EtOAc–hexane); R_f=0.42 (20% EtOAc in hexane); IR (film) 3358, 2934, 2856, 1717, 1624, 1291, 1265, 1223 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.85 (t, J=2.0 Hz, 1H), 8.40 (br d, J=6.8 Hz, 1H, –N*H*), 7.98 (d, J=8.8 Hz, 1H), 6.86 (d, J=9.2 Hz, 1H), 3.88 (s, 3H), 3.60–3.50 (m, 1H), 2.10–2.00 (m, 2H), 1.80–1.77 (m, 2H), 1.75–1.65 (m, 1H), 1.50–1.20 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 146.9, 136.1, 131.0, 129.8, 116.6, 113.8, 52.0, 51.3, 32.5 (×2), 25.4, 24.4 (×2); MS (+ESI) *m*/*z* (relative intensity) 579 ($2M+Na^+$, 100), 301 ($M+Na^+$, 98). Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.51; H, 6.51; N, 10.05.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.10.050.

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18. The crystallographic data (excluding structure factors) of **9b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 655288. Copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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