JOC Article

Smiles Rearrangements in Ugi- and Passerini-Type Couplings: New Multicomponent Access to *O*- and *N*-Arylamides

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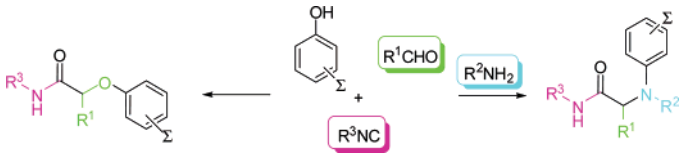

The use of Smiles rearrangement in Ugi- and Passerini-type couplings with electron-deficient phenols allows very straightforward multicomponent formation of *O*-aryl- and *N*-arylamides. Best yields were observed with the highly activated *o*- and *p*-nitrophenols, salicylic derivatives giving adducts in lower yields. The scope of these new reactions is further increased by the successful couplings of heterocyclic phenols such as hydroxypyridines and hydroxypyrimidines.

Introduction

In the drug discovery process, the development of high-throughput screening has spurred organic chemists to device new reactions affording scaffolds with increased molecular diversity and complexity. The growing interest in multicomponent reactions (MCRs)[1] and, more precisely, isocyanide-based multicomponent reactions (IMCRs)[2] is mainly associated with this trend. Besides the Mannich reaction, the most popular MCR is probably the Ugi reaction[3] (U-4CR) representing the best compromise between the search for the higher number of components and the demand for efficient and general reactions. Discovered in 1959, it allows the formation of peptide derivatives by the coupling of isocyanides with carbonyl compounds, primary amines, and carboxylic acids. It can be viewed in a way as a Mannich extension of the Passerini reaction[4] discovered some 30 years before. The efficiency of both reactions is associated with the displacement of various equilibria by an irreversible acyl transfer coined as Mumm rearrangement.[5] Changing one partner in a known multicomponent coupling is an interesting strategy for the discovery of new reactions and reactivity. When considering carboxylic acids in Ugi or Passerini MCR, their replacement represents a challenging problem because of the central role they play in the many steps of the

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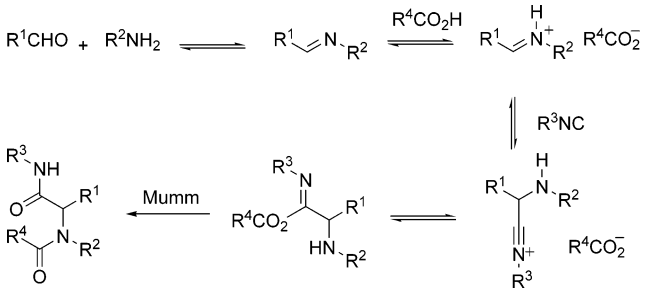
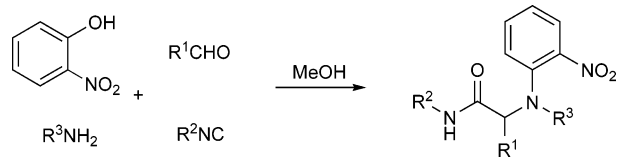
SCHEME 1. Mechanism of the Ugi Reaction



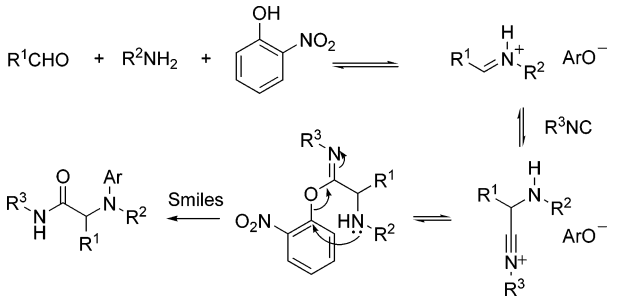
reaction mechanism. In the more complex Ugi reaction, their Bronstëd properties allow faster imine formation and addition of the moderately nucleophilic isocyanide to the activated iminium. The carboxylate is then involved in the trapping of the nitrilium species, and finally, the structure of the acid allows the Mumm rearrangement to settle and displace all the equilibria (Scheme 1). Indeed, efficient replacement of the carboxylic acids implies a new reaction mechanism and a new rearrangement takes place. In the case of the Ugi reaction, most of the potential surrogates (water, hydrazoic acid, carbonic acid monoesters, hydrogen sulfide, thiocarboxylic acids, hydrogen selenide, cyanate, thiocyanate, and thiosulfate)[6] have been examined by Ugi shortly after his pioneering description of the U-4CR reaction. In all these reactions, the irreversible Mumm-type rearrangements observed with carboxylic acids are replaced either by analogous transfer of acyl moieties (carbonic acid or thiocarboxylic acids),[7] by an irreversible tautomerization of imidate to amides (water, hydrogen sulfide, and selenide),[8] or by a final cyclization (hydrazoic acid forming tetrazoles, cyanate and thiocyanate giving hydanthoïns derivatives).[9] In the case of the Passerini reaction, similar uses of water (in the presence of mineral acids),[10] hydrazoic acid,[11] as well as thiocarboxylic acids[12] have been reported. More interestingly, stoichiometric use of $TiCl_4$ allows the formation of stable titanium complexes of chloro imidoyles which can be later hydrolyzed to α-hydroxy amides.[13]

Recently, we reported the first use of Smiles rearrangements[14] in Ugi- and Passerini-type reactions.[15] In these new multicomponent couplings, electron-deficient phenols are used as acidic partners in 3- and 4-CR leading to *O*-aryl- and *N*-arylamides (Scheme 2).

SCHEME 2. Ugi−Smiles Coupling of *o*-Nitrophenol



SCHEME 3. Steps Involved in the Ugi−Smiles Coupling of *o*-Nitrophenol



We further demonstrated that these couplings first observed with *o*- and *p*-nitrophenol could be extended to various heterocyclic derivatives sharing precedents in Smiles rearrangement.[16] In this paper, we describe our most comprehensive results on Passerini- and Ugi-type couplings with phenolic systems and discuss the nature of potential electron-withdrawing groups as well as neighboring effects observed with ortho substituents.

Results and Discussion

Ugi−Smiles Couplings. At the outset of this study, we believed that the presence of an electron-withdrawing group on phenol would increase its acidity sufficiently so that it could protonate the imine, forming a phenolate to trap the nitrilium. Furthermore, the ability of electron-withdrawing groups to trigger Smiles rearrangements on phenolic systems could afford in our case the irreversible step required for efficient Ugi-type couplings (Scheme 3).

After checking the lack of reactivity of unsubstituted phenol and *m*-nitrophenol, we observed the expected couplings with *o*- and *p*-nitrophenols under moderate heating in methanol with isocyanides (1 equiv), carbonyl compounds (1 equiv), and

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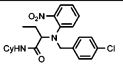
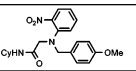
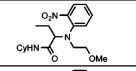
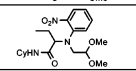
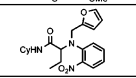
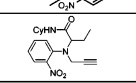
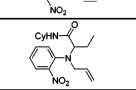
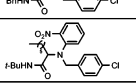
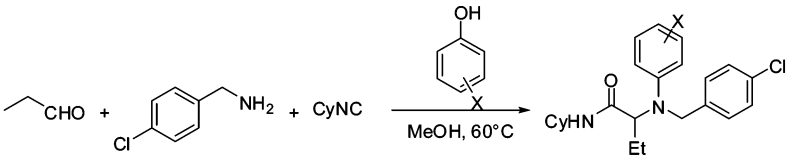
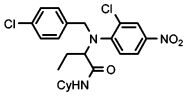
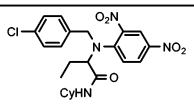
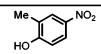
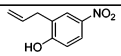
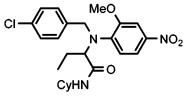
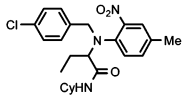
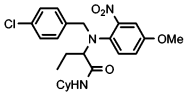
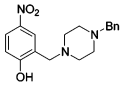
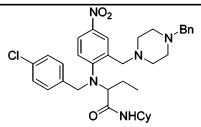
TABLE 1. Ugi−Smiles Couplings of *o*- and *p*-Nitrophenols

Entry	R^1COR'	R^2NH_2	R^3NC	Phenol	Conditions	Product	Yield (%)[a]
1			CyNC		20h (40°C)		74 (MeOH) 90 (toluene) 100 (MeOH,μW)
2			CyNC		16h (60°C)		81
3			CyNC		4h (40°C)		71
4			CyNC		16h (60°C)		64
5			CyNC		16h (60°C)		97
6			CyNC		16h (60°C)		71
7			CyNC		16h (60°C)		72
8			CyNC		(60°C)	-	-
9		Et_2NH	CyNC		(60°C)	-	-
10			CyNC		(60°C)	-	-
11			BnNC		4h (40°C)		96
12	$C_6H_{11}CHO$		*t*-BuNC		4h (40°C)		79
13					16h (60°C)		71
14					16h (60°C)		60
15			CyNC		60°C	-	-
16			CyNC		60°C	-	-
17			CyNC		20h (60°C)		80
18			CyNC		20h (60°C)		70[b]
19			CyNC		70h (60°C)		90
20			CyNC		7d (60°C)		33
21			CyNC		10d (60°C)		71
22			CyNC		16h (40°C)		72
23			*t*-BuNC		48h (60°C)		98
24			CyNC		10d (60°C)		46

[a] Isolated yields. [b] When a catalytic amount (15 mol %) of $MgClO_4$ was added, the desired adduct was formed in 81% yield.

TABLE 2. Ugi−Smiles Couplings of Substituted Nitrophenols



Entry	Phenol	Conditions	Product	Yield (%)[a]
1		16h		95
2		48h		73
3		-	-	-
4		-	-	-
5		16h		62
6		72h		96
7		72h		98
8		48h		88

[a] Isolated yields.

primary amines (1 equiv). The various amines, isocyanides, and carbonyl derivatives tested in this new Ugi−Smiles reaction are collected in Table 1. As observed in the Ugi coupling with carboxylic acids, aldehydes, and ketones are efficient partners, ketones requiring higher reaction times and giving slightly lower yields (Table 1, entries 20, 21, and 24). α,β-Unsaturated aldehydes and furfural, however, were not satisfying partners in this reaction (Table 1, entries 15 and 16). Among isocyanides tested, the benzyl derivative is the most reactive (Table 1, entry 11); the less nucleophilic isocyanoacetic acid ethyl ester can be coupled with aldehyde in good to moderate yields (Table 1, entry 14), whereas *p*-toluenesulfonyl methyl isocyanide (TosMIC) does not react at all. Anilines fail to give any coupled product (Table 1, entry 8); this could be explained by the lower nucleophilicity of the aromatic amine decreasing the efficiency of the Smiles rearrangement. Indeed, a similar effect has been observed by Smiles when comparing the reactivity of various N−H and N−Ph nitroarylsulfones.[17]

The key role of the Smiles rearrangement was further demonstrated by the absence of any adduct when secondary amines were tested under these conditions (Table 1, entry 9). Though *N*-arylated compounds could not be formed in this reaction, one might expect the formation of simple Ugi adducts as observed in the three-component coupling of secondary amines with isocyanides and aldehydes in the presence of carboxylic acids. Similarly, piperazine fails to give any arylation on the distal nitrogen group as observed for acyl migrations in Ugi reactions[18] (Table 1, entry 10), the recovery of the nitrophenol shows here again the importance of the Smiles 5-membered transition states in the efficiency of the Ugi−Smiles coupling.

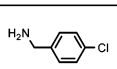
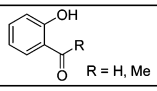
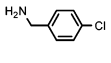
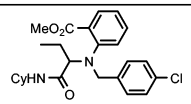
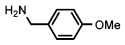
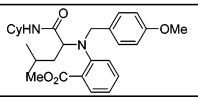
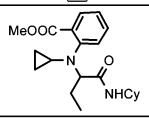
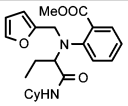
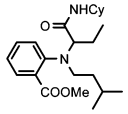
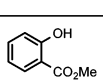
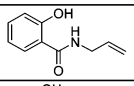
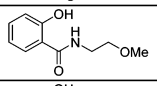
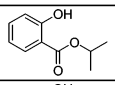
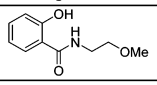
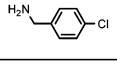
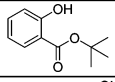
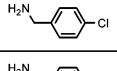
The reaction can be performed either in methanol or toluene (Table 1, entry 1) with similar yields. Several trials under microwave conditions in methanol or toluene have shown that the yields could be slightly improved with much shorter reaction time (Table 1, entry 1).

We next studied the effect of substituents on the nitrophenols (Table 2). 2,4-Dinitrophenol gives the dinitroarylamide in good yield (Table 2, entry 2). We next examined the effect of alkyl

(17) Evans, W. J.; Smiles, S. *J. Chem. Soc.* **1935**, 181−188.

(18) Giovenzana, G. B.; Tron, G. C.; Di Paola, S.; Menegotto, I. G.; Pirali, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1099−1102.

TABLE 3. Effect of Electron-Withdrawing Groups on Ugi−Smiles Couplings

Entry	R^1CHO	R^2NH_2	R^3NC	Phenol	Conditions	Product	Yield (%)[a]
1			CyNC		(60°C)	-	-
2			CyNC		48h (60°C)		74%
3			CyNC		48h (60°C)		76%
4			CyNC		20h (60°C)		56%
5			CyNC		16h (60°C)		63%
6			CyNC		48h (60°C)		47%
7			CyNC		48h (60°C)		-
8			CyNC		48h (60°C)		-
9			CyNC		48h (60°C)		-
10			CyNC		48h (60°C)	-	-
11			CyNC		(60°C)	-	-
12			CyNC		(60°C)	-	-
13			CyNC		(60°C)	-	-

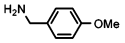
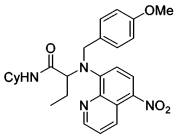
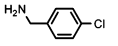
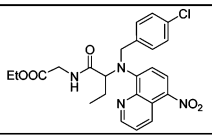
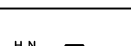
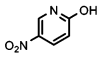
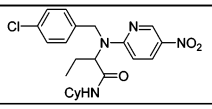
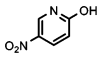
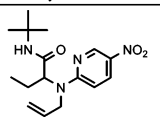
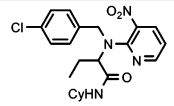
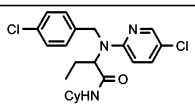
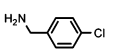
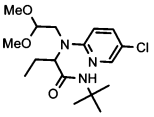
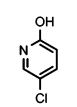
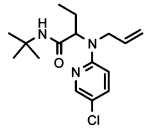
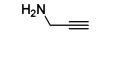
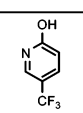
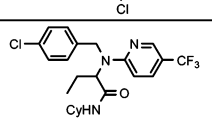
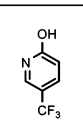
[a] Isolated yields.

substituent at the ortho position and were disappointed by the absence of reactivity of 2-methyl- and 2-allyl-4-nitrophenol showing a possible dependence of the reaction to steric hindrance (Table 2, entries 3 and 4). In contradiction with these first results, 2-chloro- and 2-methoxy-4-nitrophenols give adducts in good yields (Table 2, entries 1 and 5). To gain further insight on these aspects, a Mannich reaction was performed on 4-nitrophenol with formaldehyde and *N*-benzylpiperazine. The Mannich adduct was then submitted to Ugi−Smiles coupling with propionaldehyde, *p*-chlorobenzylamine, and cyclohexylisocyanide giving the expected adduct in 88% yield (Table 2, entry 8). Given the lack of reactivity of simple alkyl-substituted phenols, the successful couplings obtained in these last examples are in strong support of beneficial hydrogen bonding interactions in the reaction intermediates of the Ugi−Smiles coupling. Possible intramolecular hydrogen bonding in the intermediate prior to Smiles rearrangement could induce faster rearrangement by increasing the nucleophilicity of the amine.

The range of potential phenols was then screened to get a better insight of the scope of this new coupling. With 2-hydroxybenzaldehyde and 2-hydroxyacetophenone (Table 3, entry 1), preformed imines were used to suppress competition problems between the different carbonyl derivatives. The reactions were not clean, and the desired adducts could not be isolated from the mixture. Better results were obtained with salicylic acid methyl ester. Interestingly, this latter gave coupled product in the Ugi−Smiles reaction under moderate heating in methanol (Table 3, entries 2−6), whereas the para-substituted derivative was not reactive (Table 3, entry 11). However, in several instances, the formation of the corresponding amide was observed when using highly nucleophilic amines such as allylamine or 2-methoxyethylamine (Table 3, entries 7−9). *o*-Cyanophenol (Table 3, entry 12), phosphonate (Table 3, entry 13), as well as salicylic amides were not reactive.

Nitro groups are known to be the best activating group in Smiles rearrangement, good yields are thus obtained with both

TABLE 4. Ugi−Smiles Couplings of Quinoline and Pyridine Derivatives

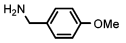
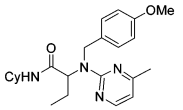
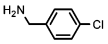
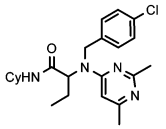
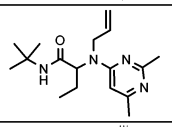
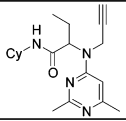
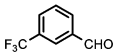
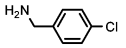
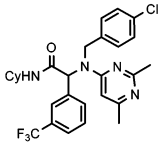
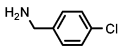
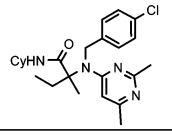
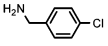
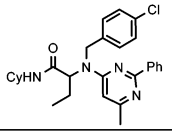
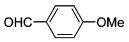
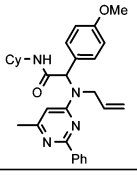
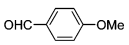
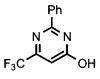
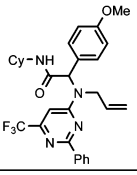
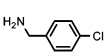
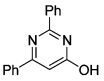
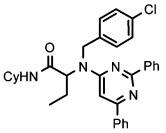
Entry	R^1CHO	R^2NH_2	R^3NC	Phenol	Conditions	Product	Yield (%)[a]
1			CyNC		48h (MeOH, 60°C)		64%
2					60h (MeOH, 60°C)		43%
3			CyNC		(MeOH, 60°C) (Toluene, 90°C)	-	-
4			CyNC		16h (MeOH, 60°C)		66%
5		$AllNH_2$	*t*-BuNC		72h (MeOH, 60°C)		96%
6			CyNC		16h (MeOH, 60°C)		62%
7			CyNC		72h (Toluene, 90°C)		27%
8			*t*-BuNC		16h (Toluene, 90°C)		14%
9		$AllNH_2$	*t*-BuNC		16h (Toluene, 90°C)		54%
10			CyNC		72h (Toluene, 90°C)		44%[b]
11		$AllNH_2$	*t*-BuNC		16h (Toluene, 90°C)		58%
12			CyNC		30min μW (Toluene, 120°C, 50W)		25%

[a] Isolated yields. [b] Only 8% in MeOH at 60 °C for 16 h.

ortho and para derivatives. The results obtained with esters give interesting clues for the mechanism of the Ugi−Smiles reaction as the pK_a difference between the ortho and the para derivative is opposite to what is expected from their reactivity. Indeed, from a simple correlation between the acidity and the ability of phenol to trigger this coupling one would expect the more acidic para-substituted ester to be more reactive (salicylic acid methyl ester: pK_a = 10.06; *p*-hydroxybenzoic acid methyl ester: pK_a = 8.34). Dealing with Ugi-type reactions, the reactivity pattern must be analyzed in light of the various steps of the mechanism with special focus on the irreversible one. In our case, as noted above for the ortho substituent effect on nitrophenols, similar hydrogen-bonding-type interactions between the ortho ester and the amino group bring additional electrophilic activation of the aromatic ring toward the nucleophilic amine in the Smiles rearrangement.

Smiles rearrangements, initially described on substituted benzene rings, were further extended to heteroaromatic com-

TABLE 5. Ugi−Smiles Couplings of Pyrimidine Derivatives

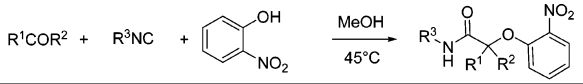
Entry	R^1CHO	R^2NH_2	R^3NC	Phenol	Conditions	Product	Yield (%)[a]
1			CyNC		15h (60°C)		38%
2			CyNC		72h (60°C)		78%
3		$AllNH_2$	*t*-BuNC		4d (60°C)		60%
4			CyNC		20min μW (80°C, 50W).		60%
5			CyNC		4d (60°C)		50%
6			CyNC		8d (60°C)		54%
7			CyNC		16h (60°C)		89%
8		$AllNH_2$	CyNC		72h (60°C)		30%[b]
9		$AllNH_2$	CyNC		72h (60°C)		51%[b]
10			CyNC		72h (60°C)		51%
11			CyNC		72h (60°C)		63%

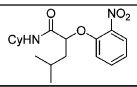
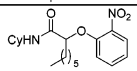
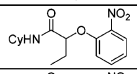
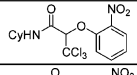
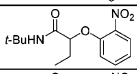
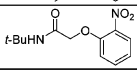
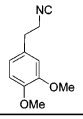
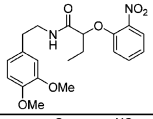
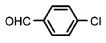
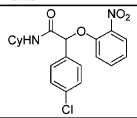
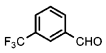
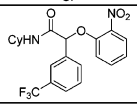
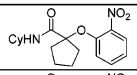
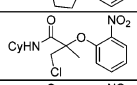
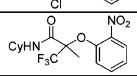
[a] Isolated yields. [b] Done with a catalytic amount (15 mol %) of $MgClO_4$.

pounds and the many examples performed later on pyridines, pyrimidines, and various azoles have largely overshadowed these initial studies. An electron-withdrawing group tethered onto the aromatic ring is not needed as the carbon bearing the hydroxyl group is now activated by the heterocyclic nitrogen atoms at either the 2 or 4 position.

We thus examined the reactivity of pyridines and pyrimidines (Tables 4 and 5) with their electronic properties dominated by

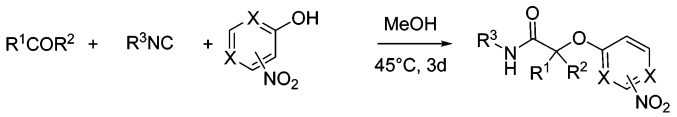
TABLE 6. Passerini−Smiles Couplings of Electron-Poor Phenols

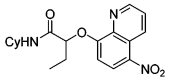
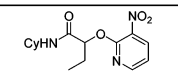
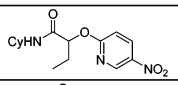
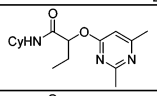
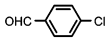
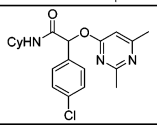


Entry	R^1COR^2	R^3NC	Phenol	Time	Product	Yield (%)[a]
1		CyNC		3d		64
2	$C_6H_{13}CHO$	CyNC		3d		64
3		CyNC		3d		80
4		CyNC		3d		50
5		*t*-BuNC		3d		36
6	H_2CO	*t*-BuNC		3d		27
7				3d		28
8		CyNC		3d		57
9		CyNC		3d		62
10		CyNC		-	-	-
11		CyNC		5d		26
12		CyNC		5d		71
13		*t*-BuNC		5d		74
14		CyNC		3d		74
15		CyNC		3d		72
16		CyNC		3d		29
17		CyNC		3d		72[b,c]
18		CyNC		3d		65
19		CyNC		3d		68
20		CyNC		-	-	-
21		CyNC		-	-	-

[a] Isolated yields. [b] 1 equiv of *N*,*N*-dimethylpiperazine was added to the reaction mixture. [c] 2 equiv of the aldehyde were used in this reaction.

TABLE 7. Passerini−Smiles Couplings of Six-Membered Ring Nitrogen Heterocycles



Entry	R^1COR^2	R^3NC	Phenol	Product	Yield (%)[a]
1		CyNC			60
2		CyNC			46[b]
3		CyNC			43[b]
4		CyNC			60
5		CyNC			24

[a] Isolated yields. [b] 1 equiv of *N,N*-dimethylpiperazine was added to the reaction mixture.

the electron-withdrawing nature of the nitrogen atom. 2-Hydroxypyridine is not reactive under these conditions (Table 4, entry 3), whereas 3- and 5-nitro-substituted 2-hydroxypyridines react smoothly by moderate heating in methanol (Table 4, entries 4−6). Less activated 5-chloro- (Table 4, entries 7−9) and 5-trifluoromethyl-substituted (Table 4, entries 10−12) 2-hydroxypyridine require higher temperature and the use of toluene as solvent to give adducts in satisfying yields.

Pyrimidines are even more activated than pyridines toward nucleophilic attacks. These heterocycles are key compounds in many biological systems with active compounds such as thymine or cytosine. They have been reported to be potent therapeutic agents for the treatment of inflammatory diseases (asthma, rheumatoid arthritis, etc.),[19] HBV infection,[20] Creutzfeldt−Jacob disease,[21] epilepsy, and cancer.[22] Consequently, such heterocyclic compounds remain major targets for the pharmaceutical industry. 4-Hydroxypyrimidines are readily prepared by the condensation of β-keto esters with amidine derivatives.[23] When submitted to the Ugi−Smiles coupling, the desired adducts were obtained in moderate to good yields under heating in methanol at 60 °C. The reactivity of 4-hydroxypyrimidines appears to be quite general: aryl-, alkyl-, and trifluoromethyl-substituted pyrimidines behave similarly (Table 5). With propargylamine as amino partner, the 4-aminopyrimidine could be only formed under microwave conditions (Table 5, entry 4) as observed for the coupling with the pyridine derivative (Table 4, entry 12). 2-Hydroxypyrimidines are also potent partners in this multicomponent reaction. The free pyrimidine, generated in situ from its commercial hydrochloride (1 equiv of NaOMe in MeOH), gave the expected 2-aminopyrimidine in moderate yield (Table 5, entry 1).

We next tested the behavior of various five-membered ring heterocyclic hydroxy derivatives. These latter (isoxazole, tetrazole, benzoxazole, and benzothiazole) were not sufficiently reactive though the well-documented use of tetrazoles in the Smiles rearrangement of the Julia−Kocienski reactions.[24]

Passerini−Smiles Couplings. Due to the higher electrophilicity of the iminium toward the aldehyde, the Passerini reaction usually requires stronger acidic conditions than the related Ugi coupling to give the desired adducts efficiently. We recently disclosed that phenolic derivatives were sufficiently acid to replace carboxylic acids in the 3-CR.[15b] Various aldehydes and ketones were coupled with *o*-nitrophenol (1 equiv) and isocyanides (1 equiv) forming α-hydroxyamides with lower yields than in the related Ugi−Smiles reaction (Table 6). The overall reactivity pattern is similar to the one observed for the Ugi coupling of phenols: aliphatic aldehydes being the most reactive (Table 6, entries 1−6) and ketones giving adducts in low yields unless activated by electron-withdrawing groups (Table 6, entries 11−13). Various substituted *o*-nitrophenols were tested successfully in this new 3-CR (Table 6, entries 14−16). Surprisingly, under the same experimental conditions, *p*-nitrophenol was not reactive reminding us of the ortho substituent effects already observed in the Ugi−Smiles coupling. Indeed, the addition of an amino methylene moiety on *p*-nitrophenol allows the reaction to proceed smoothly (Table 6, entry 18). To test whether this effect could be due to the presence of an additional

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base, 1 equiv of an amino base (triethylamine and *N*,*N*′-dimethylpiperazine) was added in the reaction mixture. The best results were obtained with *N*,*N*′-dimethylpiperazine giving the Passerini−Smiles adduct in a 26% yield. The major product (48%) obtained in this reaction is an acetal involving 2 equiv of the aldehyde for one phenol (Table 6, entry 17). In this case, the Smiles rearrangement probably failed, hydrolysis of the imidoyl moiety provides the alcohol which further attacks a second aldehyde followed by coupling with phenol. When forcing the reaction with 2 equiv of carbonyl compounds, the acetal is formed in an improved 72% yield. However, aromatic aldehydes behave differently and, with 1 equiv of *N*,*N*-dimethylpiperazine, they mainly provide the desired adduct (ratio acetal/passerini product: 1:10). In this case, raising the temperature to 70 °C in toluene is necessary for completion of the reaction (Table 6, entry 19). Less reactive 2- and 4-hydroxybenzoic acid methyl esters do not give any coupling with or without piperazine (Table 6, entries 20 and 21).

As observed for the Ugi−Smiles coupling, the reaction could be extended to heterocyclic derivatives. 4-Hydroxypyrimidines have been successfully coupled with carbonyl compounds and isocyanides in moderate to good yields. For 2-hydroxypyridines, the yields are generally improved by using 1 equiv of *N*,*N*-dimethylpiperazine (from 32% to 46% in the case of 2-hydroxy-3-nitropyridine).

Conclusion

In conclusion, we have described the first general *N*-arylations in Ugi and Passerini reactions using phenols as acidic components in place of the traditional carboxylic acids. The efficiency of these processes is linked to an irreversible Smiles rearrangement in the last step of the mechanism. The displacement of equilibria by irreversible rearrangement or cyclization is a general principle that has already allowed significant recent developments in isocyanide based multicomponent reactions.[25] The Ugi reaction has nearly reached its half century of existence, and the Passerini reaction is even older. One might assume from their age that these reactions are now mature and that most developments concerning these fields can only be associated with post-condensations using more recent chemistry. The successful couplings of phenols described herein give additional clues to the wealth of unrevealed chemistry hidden at the heart of these two reactions.

Experimental Section

All of the reactions were performed under nitrogen atmosphere using reagent-grade solvents and starting materials without further purification. These reactions are not moisture sensitive.

General Procedure for Phenol-Induced Ugi-4CR. To a 1 M solution of the aldehyde (1 mmol) in methanol was added successively 1.0 equiv of amine, 1.0 equiv of isocyanide, and 1.0 equiv of phenol under inert atmosphere. The resulting mixture was stirred until completion (TLC). It was then concentrated in vacuo, and the crude product was purified by flash chromatography on silica gel.

2[(4-Chlorobenzyl)-(2-nitrophenyl)amino]-*N*-cyclohexylbutyramide (Table 1, entry 1): yellow solid; yield (20 h at 40 °C in MeOH) 74%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (dd, 1H, J = 8.1, 1.5 Hz), 7.42 (td, 1H, J = 7.6, 1.5 Hz), 7.22−7.12 (m, 4H), 7.04 (d, 1H, J = 9.4 Hz), 6.76 (d, 1H, J = 9.4 Hz), 4.30 (d, 1H, J = 14.9 Hz), 4.12 (d, 1H, J = 14.9 Hz), 3.84−3.74 (m, 1H), 3.60 (dd,1H, J = 8.6, 5.3 Hz), 1.98−1.87 (m, 2H), 1.88−1.79 (m, 2H), 1.77−1.64 (m, 4H), 1.43−1.08 (m, 4H), 0.90 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.8, 142.3, 138.5, 135.3, 133.7, 133.1, 130.1, 129.1, 126.4, 125.6, 124.8, 69.8, 48.3, 43.8, 33.5, 33.2, 25.9, 25.1, 23.4, 11.4; IR (thin film) 3318, 2930, 1635, 1558, 1349, 1090 cm^{-1}; MS (DI, CI NH_3) *m*/*z* 431; mp 158 °C. Anal. Calcd for $C_{23}H_{28}ClN_3O_3$: C, 64.25; H, 6.56. Found: C, 64.17; H, 6.52.

2-(*N*-(4-Methoxybenzyl)-*N*-(2-nitrophenyl)amino)-*N*-cyclohexylacetamide (Table 1, entry 2): orange oil; yield (16 h at 60 °C in MeOH) 81%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (d, 1H, J = 8.3 Hz), 7.49 (t, 1H, J = 7.6 Hz), 7.35 (br s, 1H), 7.21−7.13 (m, 2H), 6.99 (d, 2H, J = 8.6 Hz), 6.82 (d, 2H, J = 8.6 Hz), 4.04 (s, 2H), 3.83−3.69 (m, 1H), 3.79 (s, 3H) 3.75 (s,2H), 1.85−1.53 (m, 4H), 1.40−1.07 (m, 6H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 168.5, 159.8, 143.6, 133.9, 130.5, 127.7, 126.1, 124.1, 123.9, 114.4, 60.1, 55.7, 55.2, 48.3, 33.2, 25.8, 25.1; IR (thin film) 3368, 2933, 2855, 1672, 1519, 1253 cm^{-1}; MS (DI, CI NH_3) *m*/*z* 397; HRMS calcd for $C_{22}H_{27}N_3O_4$ 397.2002, found 397.2015.

***N*-Cyclohexyl-2-[(2-methoxyethyl)-(2-nitrophenyl)amino]butyramide (Table 1, entry 3):** yellow oil; yield (4 h at 40 °C in MeOH) 71%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (dd, 1H, J = 8.1, 1.5 Hz), 7.50 (td, 1H, J = 7.6, 1.5 Hz), 7.43 (br s, 1H), 7.31 (dd, 1H, J = 7.6, 1.0 Hz), 7.17 (ddd, 1H, J = 8.1, 7.6, 1.0 Hz), 3.81−3.72 (m, 1H), 3.69 (t, 1H, J = 6.8 Hz), 3.40−3.28 (m, 4H), 3.22 (s, 3H), 2.06−1.96 (m, 2H), 1.93−1.79 (m, 2H), 1.77−1.66 (m, 4H), 1.42−1.06 (m, 4H), 0.93 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 172.2, 146.9, 142.9, 133.1, 125.9, 125.5, 124.1, 70.1, 69.6, 59.1, 49.9, 48.4, 33.2, 33.1, 26.0, 25.3, 24.0, 11.7. IR (thin film) 3332, 2936, 1654, 1522, 1359, 1119 cm^{-1}; MS (DI, CI NH_3) *m*/*z* 364. Anal. Calcd for $C_{19}H_{29}N_3O_4$: C, 62.79; H, 8.04. Found: C, 62.61; H, 8.28.

2-(*N*-(4-Chlorobenzyl)-*N*-(2-chloro-4-nitrophenyl)amino)-*N*-cyclohexylbutanamide (Table 2, entry 1): brown oil; yield (16 h at 60 °C in MeOH) 95%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (d, 1H, J = 2.3 Hz), 7.37 (dd, 1H, J = 8.8, 2.3 Hz), 7.21 (d, 2H, J = 8.3 Hz), 7.15 (d, 1H, J = 8.8 Hz), 7.05 (d, 2H, J = 8.3 Hz), 6.58 (br s, 1H), 4.30 (d, 1H, J = 14.1 Hz), 4.15 (d, 1H, J = 14.1 Hz), 3.85−3.74 (m, 1H), 3.54 (dd, 1H, J = 5.5, 4.3 Hz), 1.98−1.80 (m, 2H), 1.77−1.57 (m, 4H), 1.46−1.08 (m, 6H), 0.90 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.2, 147.0, 141.2, 133.8, 134.9, 133.1, 130.1, 129.9, 129.2, 127.6, 125.5, 69.8, 53.8, 48.4, 33.8, 33.2, 25.8, 25.1, 23.4, 11.5; IR (thin film) 3311, 2933, 2858, 1659, 1525, 1346, 1094 cm^{-1}; MS (DI, CI NH_3) *m*/*z* 465; HRMS calcd for $C_{23}H_{27}Cl_2N_3O_3$ 463.1429, found 463.1436.

2-(*N*-(4-Chlorobenzyl)-*N*-(2,4-dinitrophenyl)amino)-*N*-cyclohexylbutanamide (Table 2, entry 2): orange oil; yield (48 h at 60 °C in MeOH) 73%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.61 (d, 1H, J = 3.0 Hz), 8.18 (dd, 1H, J = 9.1, 3.0 Hz), 7.28−7.24 (m, 2H), 7.21−7.16 (m, 3H), 6.23 (d, 1H, J = 8.3 Hz), 4.60 (d, 1H, J = 16.2 Hz), 4.52 (d, 1H, J = 16.2 Hz), 3.82−3.74 (m, 1H), 3.71 (t, 1H, J = 7.3 Hz), 2.22−2.12 (m, 1H), 1.94−1.81 (m, 1H), 1.77−1.57 (m, 4H), 1.42−1.04 (m, 6H), 0.93 (t, 3H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 168.5, 148.6, 141.1, 140.4, 134.2, 134.1, 129.6, 129.3, 129.0, 123.2, 123.0, 70.2, 51.2, 48.9, 33.3, 33.2, 25.8, 25.1, 24.1, 12.0; IR (thin film) 3321, 2933, 2858, 1659, 1603, 1531, 1324 cm^{-1}; MS (DI, CI NH_3) *m*/*z* 476; HRMS calcd for $C_{23}H_{27}ClN_4O_5$ 474.1670, found 474.1673.

2-[(4-Chlorobenzyl)-(1-cyclohexylcarbamoylpropyl)amino]-benzoic acid methyl ester (Table 3, entry 2): yellow oil; yield (48 h at 60 °C in MeOH) 74%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (br s 1H), 7.62 (dd, 1H, J = 7.6, 1.7 Hz), 7.32 (td, 1H, J = 7.8, 1.7 Hz), 7.16−7.01 (m, 6H), 4.19 (d, 1H, J = 14.6 Hz), 4.04 (d, 1H, J = 14.6 Hz), 3.85 (s, 3H), 3.84−3.74 (m, 1H), 3.60 (dd,-1H, J = 8.6, 5.3 Hz), 1.90−1.78 (m, 2H), 1.73−1.53 (m, 2H), 1.40−1.27 (m, 4H), 1.26−1.14 (m, 4H), 0.82 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 171.9, 168.5, 148.9, 136.4, 133.1,

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132.9, 132.5, 131.3, 130.2, 128.6, 125.1, 124.1, 70.8, 54.4, 52.6, 48.1, 33.5, 33.2, 25.9, 25.1, 22.9, 11.6; IR (thin film) 3338, 2932, 2853, 1717, 1674, 1449, 1086 cm^{-1}; MS (DI, CI NH_3) *m*/*z* 444. Anal. Calcd for $C_{25}H_{31}ClN_2O_3$: C, 67.78; H, 7.05. Found: C, 67.59; H, 7.13.

2-[(1-Cyclohexylcarbamoyl-3-methylbutyl)-(4-methoxybenzyl)-amino]benzoic acid methyl ester (Table 3, entry 3): yellow oil; yield (48 h at 60 °C in MeOH) 76%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (br s, 1H), 7.63 (d, 1H, J = 7.8 Hz), 7.31−7.27 (m, 1H), 7.15−7.05 (m, 3H), 7.03−6.97 (td, 1H, J = 7.8, 1.7 Hz), 6.74 (dd, 2H, J = 7.8, 1.7 Hz), 4.27 (d, 1H, J = 14.6 Hz), 4.01 (d, 1H, J = 14.6 Hz), 3.88 (s, 3H), 3.84−3.73 (m, 2H), 3.74 (s, 3H), 1.97−1.74 (m, 4H), 1.73−1.50 (m, 2H), 1.45−1.12 (m, 7H), 0.75 (d, 3H, J = 6.6 Hz), 0.72 (d, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 172.3, 168.8, 158.8, 149.2, 132.3, 131.2, 130.0, 129.6, 127.5, 124.3, 123.2, 113.9, 67.8, 55.5, 52.9, 52.6, 48.2, 38.2, 33.4, 33.2, 26.0, 25.9, 25.2, 25.1, 23.4, 22.4; IR (thin film) 3358, 2929, 2843, 1719, 1672, 1462, 1095 cm^{-1}; MS (DI, CI NH_3) *m*/*z* 468. Anal. Calcd for $C_{28}H_{38}N_2O_4$: C, 72.07; H, 8.21. Found: C, 71.85; H, 8.43.

Methyl 2-(*N*-(1-(cyclohexylcarbamoyl)propyl)-*N*-cyclopropyl-amino)benzoate (Table 3, entry 4): white oil; yield (20 h at 60 °C in MeOH) 56%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (dd, 1H, J = 7.8, 1.5 Hz), 7.40−7.34 (m, 2H), 7.17 (d, 1H, J = 7.8 Hz), 7.01 (t, 1H, J = 7.8 Hz), 3.91 (s, 3H), 3.81 (dd, 1H, J = 5.8, 3.8 Hz), 3.76−3.65 (m, 1H), 2.61−2.51 (m, 1H), 2.17−2.06 (m, 1H), 1.96−1.81 (m, 1H), 1.74−1.53 (m, 4H), 1.40−1.08 (m, 6H), 0.95 (t, 3H, J = 7.3 Hz), 0.67−0.59 (m, 1H), 0.58−0.46 (m, 2H), 0.41−0.34 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 171.5, 169.4, 150.7, 132.5, 130.6, 125.9, 123.6, 122.1, 69.8, 52.6, 48.3, 33.3, 33.0, 32.9, 25.9, 25.3, 23.1, 11.9, 9.2, 8.5; IR (thin film) 3324, 2936, 2858, 1719, 1665, 1534, 1490, 1453, 1087 cm^{-1}; MS (DI, CI NH_3) *m*/*z* 359; HRMS calcd for $C_{21}H_{30}N_2O_3$ 358.2257, found 358.2254.

General Procedure for Aminopyrimidine or Aminopyridine Derivative Synthesis. To a 1 M solution of carbonyl compound (1 mmol) in methanol or toluene were added the amine (1.0 equiv), the isocyanide (1.0 equiv), and the hydroxypyrimidine or hydroxypyridine (1.0 equiv). The resulting mixture was stirred at 60 or 90 °C under an inert atmosphere and concentrated in vacuo. The crude product was then purified by flash chromatography on silica gel to give the desired adduct.

2-(*N*-(4-Chlorobenzyl)-*N*-(5-nitropyridin-2-yl)amino)-*N*-cyclohexylbutanamide (Table 4, entry 4): yellow solid; yield (16 h at 60 °C in MeOH) 66%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.10 (d, 1H, J = 2.7 Hz), 8.15 (dd, 1H, J = 9.3, 2.7 Hz), 7.33−7.28 (m, 2H), 7.14 (d, 2H, J = 8.3 Hz), 6.33 (d, 1H, J = 9.3 Hz), 6.22 (d, 1H, J = 7.8 Hz), 5.27 (t,1H, J = 7.1 Hz), 4.87 (d, 1H, J = 17.4 Hz), 4.75 (d, 1H, J = 17.4 Hz), 3.78−3.67 (m, 1H), 2.17−2.06 (m, 1H), 1.95−1.86 (m, 1H), 1.77−1.54 (m, 4H), 1.46−1.09 (m, 6H), 0.95 (t, 3H, J = 7.7 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 169.4, 161.2, 146.0, 136.4, 135.7, 133.6, 133.5, 129.5, 128.0, 107.2, 61.0, 49.5, 48.5, 33.4, 33.1, 25.8, 25.0, 24.9, 22.7, 11.3; IR (thin film) 3320, 2932, 2857, 1665, 1593, 1496, 1296, 1121 cm^{-1}; MS (DI, CI NH_3) *m*/*z* 432; HRMS calcd for $C_{22}H_{27}ClN_4O_3$ 430.1772, found 430.1780; mp 119 °C.

2-(*N*-(4-Chlorobenzyl)-*N*-(5-chloropyridin-2-yl)amino)-*N*-cyclohexylbutanamide (Table 4, entry 7): white solid; yield (72 h at 90 °C in toluene) 27%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.13 (d, 1H, J = 2.5 Hz), 7.33 (dd, 1H, J = 8.8, 2.5 Hz), 7.28 (d, 2H, J = 8.6 Hz), 7.16 (d, 2H, J = 8.6 Hz), 6.49 (d, 1H, J = 8.1 Hz), 6.26 (d, 1H, J = 8.8 Hz), 5.05 (dd, 1H, J = 8.6, 6.3 Hz), 4.73 (d, 1H, J = 17.7 Hz), 4.53 (d, 1H, J = 17.7 Hz), 3.76−3.67 (m, 1H), 2.14−2.02 (m, 1H), 1.92−1.84 (m, 1H), 1.72−1.50 (m, 6H), 1.45−1.06 (m, 4H), 0.92 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.6, 157.2, 145.9, 137.8, 137.3, 133.1, 129.2, 128.1, 120.8, 109.3, 60.7, 49.5, 48.1, 33.3, 33.1, 25.9, 24.8, 22.5, 11.5; IR (thin film) 3311, 2937, 2854, 1665, 1477, 1496, 1273 cm^{-1}; MS (DI, CI NH_3) *m*/*z* 420; HRMS calcd for $C_{22}H_{27}Cl_2N_3O$419.1531, found 419.1533; mp 143 °C.

2-(*N*-(4-Chlorobenzyl)-*N*-(5-(trifluoromethyl)pyridin-2-yl)-amino)-*N*-cyclohexylbutanamide (Table 4, entry 10): white solid; yield (72 h at 90 °C in toluene) 44%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.44 (d, 1H, J = 2.5 Hz), 7.57 (dd, 1H, J = 8.8, 2.5 Hz), 7.30 (d, 2H, J = 8.6 Hz), 7.15 (d, 2H, J = 8.6 Hz), 6.42 (d, 1H, J = 7.8 Hz), 6.36 (d, 1H, J = 8.8 Hz), 5.19 (dd, 1H, J = 8.8, 6.3 Hz), 4.80 (d, 1H, J = 17.6 Hz), 4.63 (d, 1H, J = 17.6 Hz), 3.78−3.67 (m, 1H), 2.16−2.04 (m, 1H), 1.93−1.84 (m, 1H), 1.75−1.50 (m, 6H), 1.46−1.25 (m, 3H), 1.22−1.09 (m, 1H), 0.94 (t, 3H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.2, 160.4, 145.4, 136.7, 135.1, 133.3, 129.3, 128.1, 123.5, 116.4, 107.8, 60.4, 49.2, 48.3, 33.3, 33.1, 25.8, 24.9, 22.5, 11.5; IR (thin film) 3321, 2933, 2864, 1672, 1529, 1318, 1135 cm^{-1}; MS (DI, CI NH_3) *m*/*z* 453; HRMS calcd for $C_{23}H_{27}ClF_3N_3O$ 453.1795, found 453.1797; mp 141 °C.

***N*-Cyclohexyl-2-[(4-methoxybenzyl)-(4-methylpyrimidin-2-yl)-amino]butyramide (Table 5, entry 1):** white solid; yield (15 h at 60 °C in MeOH with 1 equiv of MeONa) 38%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.23 (d, 1H, J = 5.3 Hz), 7.28 (d, 2H, J = 8.1 Hz), 6.82 (d, 2H, J = 8.1 Hz), 6.47 (d, 1H, J = 5.3 Hz), 6.44 (br s, 1H, NH), 5.02 (d, 1H, J = 15.6 Hz), 4.72 (t,1H, J = 7.3 Hz), 4.64 (d, 1H, J = 15.6 Hz), 3.79 (s, 3H), 3.69−3.58 (m, 1H), 2.37 (s, 3H), 1.89−1.70 (m, 2H), 1.64−1.44 (m, 2H), 1.38−1.18 (m, 4H), 1.17−0.93 (m, 4H), 0.85 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 171.2, 167.7, 162.3, 158.9, 157.6, 132.3, 129.5, 114.1, 110.5, 61.9, 55.6, 48.8, 47.9, 33.1, 32.9, 25.9, 24.9, 24.8, 22.3, 11.6; IR (thin film) 3311, 2936, 2864, 1669, 1582, 1516, 1472, 1360, 1275 cm^{-1}; MS (DI, CI NH_3) *m*/*z* 396; HRMS calcd for $C_{23}H_{32}N_4O_2$ 396.2525, found 396.2511; mp 87 °C.

2-(*N*-(4-Chlorobenzyl)-*N*-(2,6-dimethylpyrimidin-4-yl)amino)-*N*-cyclohexylbutanamide (Table 5, entry 2): colorless oil; yield (72 h at 60 °C in MeOH) 78%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 (d, 2H, J = 8.3 Hz), 7.13 (d, 2H, J = 8.3 Hz), 6.71 (br s, 1H), 5.95 (s, 1H), 5.12 (br s,1H), 4.72 (d, 1H, J = 17.9 Hz), 4.52 (d, 1H, J = 17.9 Hz), 3.75−3.65 (m, 1H), 2.56 (s, 3H), 2.26 (s, 3H), 2.13−1.99 (m, 2H), 1.93−1.83 (m, 1H), 1.73−1.49 (m, 4H), 1.46−1.06 (m, 5H), 0.90 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.1, 166.6, 166.3, 163.2, 136.7, 133.2, 129.3, 128.0, 100.7, 59.8, 48.6, 48.1, 33.4, 33.1, 26.6, 25.9, 24.9, 24.8, 24.7, 22.3, 11.4; IR (thin film) 3338, 2940, 2856, 1680, 1596, 1489, 1355, 1282 cm^{-1}; MS (DI, CI NH_3) *m*/*z* 415; HRMS calcd for $C_{23}H_{31}ClN_4O$ 414.2186, found 414.2179.

2-(*N*-Allyl-*N*-(2,6-dimethylpyrimidin-4-yl)amino)-*N*-*tert*-butylbutanamide (Table 5, entry 3): colorless oil; yield (4 d at 60 °C in MeOH) 60%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.78 (s, 1H), 6.14 (s, 1H), 5.79 (ddt, 1H, J = 17.6, 10.3, 4.5 Hz), 5.19 (dd, 1H, J = 17.6, 1.7 Hz), 5.17 (dd, 1H, J = 10.3, 1.7 Hz), 5.06 (br s, 1H), 4.09 (dd, 1H, J = 17.6, 4.5 Hz), 3.86 (dd, 1H, J = 17.6, 4.5 Hz), 2.52 (s, 3H), 2.36 (s, 3H), 2.11−2.00 (m, 1H), 1.74−1.62 (m, 1H), 1.27 (s, 9H), 0.90 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.6, 166.5, 165.7, 162.9, 133.9, 117.3, 170.8, 59.7, 51.2, 47.5, 29.1, 24.8 et 24.7, 21.8, 11.3; IR (thin film) 3365, 2946, 2859, 1670, 1506, 1285, 1126 cm^{-1}; MS (DI, CI NH_3) *m*/*z* 305; HRMS calcd for $C_{17}H_{28}N_4O$ 304.2263, found 304.2260.

General Procedure for Phenol-Induced Passerini-3CR. To a 1 M solution of the aldehyde (1mmol) in methanol were added successively 1.0 equiv of isocyanide and 1.0 equiv of phenol under inert atmosphere. The resulting mixture was stirred until completion (TLC). It was then concentrated in vacuo, and the crude product was purified by flash chromatography on silica gel.

2-(2-Nitrophenoxy)-*N*-cyclohexyl-4-methylpentanamide (Table 6, entry 1): yellow solid; yield 64%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (dd, 1H, J = 8.4, 1.8 Hz), 7.55 (td, 1H, J = 8.4, 1.8 Hz), 7.12−7.08 (m,2H), 6.97 (br s, 1H), 4.85 (dd, 1H, J = 7.8, 3.9 Hz), 3.78−3.69 (m, 1H), 1.96−1.88 (m, 2H), 1.76−1.63 (m, 2H), 1.63−1.52 (m, 2H), 1.40−1.11 (m, 7H), 0.97 (d, 3H, J = 6.2 Hz), 0.93 (d, 3H, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 169.9, 150.9, 140.3, 135.0, 126.4, 121.8, 115.1, 78.9, 48.2, 41.8, 33.1, 25.8, 25.0,

24.9, 23.5, 22.5; IR (thin film) 1670, 1592, 1530, 1485, 1360, 1255, 1059 cm^{-1}; MS (DI, CI NH_3) *m*/*z* 335; HRMS calcd for $C_{18}H_{26}N_2O_4$ 334.1893, found 334.1893; mp 72 °C.

2-(2-Nitrophenoxy)-*N*-cyclohexyloctanamide (Table 6, entry 2): yellow solid; yield 64%; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.91 (dd, 1H, J = 8.4, 1.6 Hz), 7.56 (td, 1H, J = 8.4, 1.6 Hz), 7.12−7.08 (m,3H), 4.86 (t, 1H, J = 5.1 Hz), 3.82−3.73 (m, 1H), 2.03−1.97 (m, 2H), 1.76−1.70 (m, 2H), 1.67−1.55 (m, 2H), 1.46−1.37 (m, 2H), 1.36−1.06 (m, 12H), 0.86 (t, 3H, J = 6.1 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 169.3, 151.0, 140.1, 135.1, 126.6, 121.7, 115.3, 79.9, 48.3, 33.2, 33.0, 32.6, 31.9, 29.4, 25.8, 25.0, 24.6, 22.9, 14.4; IR (thin film) 2978, 1665, 1592, 1530, 1255, 1064 cm^{-1}; MS (DI, CI NH_3) *m*/*z* 362; HRMS calcd for $C_{20}H_{30}N_2O_6$ 362.2206, found 362.2205; mp 70 °C.

2-(2-Nitrophenoxy)-*N*-cyclohexylbutanamide (Table 6, entry 3): yellow solid; yield 80%; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.92 (dd, 1H, J = 8.3, 1.2 Hz), 7.56 (td, 1H, J = 8.3, 1.2 Hz), 7.13 (br s, 1H), 7.09 (t,2H, J = 8.3 Hz), 4.85 (t, 1H, J = 4.9 Hz), 3.84−3.73 (m, 1H), 2.09−2.02 (m, 2H), 1.77−1.55 (m, 4H), 1.43−1.08 (m, 6H), 0.99 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 169.0, 151.0, 140.1, 135.2, 126.7, 121.7, 115.3, 81.0, 48.6, 33.3, 33.0, 25.8, 25.6, 25.0, 8.8; IR (thin film) 1670, 1530, 1490, 1350, 1250, 1070 cm^{-1}; MS (DI, CI NH_3) *m*/*z* 307; HRMS calcd for $C_{16}H_{22}N_2O_4$ 306.1580, found 306.1584; mp 89 °C.

2-(5-Nitroquinolin-8-yloxy)-*N*-cyclohexylbutanamide (Table 7, entry 1): yield 60%; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.25 (dd, 1H, J = 8.8, 1.6 Hz), 9.08 (dd, 1H, J = 4.2, 1.6 Hz,), 8.52 (d, 1H, J = 8.8 Hz), 7.77 (dd, 1H, J = 8.8, 4.2 Hz), 7.22 (d, 1H, J = 8.8 Hz), 7.72 (br s, 1H), 4.85 (dd,1H, J = 7.4, 4.3 Hz), 3.84−3.72 (m, 1H), 2.25−2.17 (m, 1H), 2.34−2.26 (m, 1H), 2.02−1.84 (m, 2H), 1.78−1.70 (m, 2H), 1.65−1.57 (m, 2H), 1.45−1.24 (m, 4H), 1.00 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 169.8, 160.0, 150.9, 140.7, 139.4, 133.3, 127.5, 125.3, 123.6, 111.0, 84.6, 48.4, 33.4, 33.1, 26.8, 25.9, 25.1, 25.0, 10.3; MS (DI, CI NH_3) *m*/*z* 358; IR (thin film) 2930, 2360, 1652, 1560, 1503, 1332 cm^{-1}; HRMS calcd for $C_{19}H_{23}N_3O_4$ 357.1689, found 357.1696.

2-(3-Nitropyridin-2-yloxy)-*N*-cyclohexylbutanamide (Table 7, entry 2): orange solid; yield 43%; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.05 (d, 1H, J = 2.8 Hz), 8.42 (dd, 1H, J = 9.1, 2.8 Hz), 6.96 (d, 1H, J = 9.1 Hz), 5.98 (br s, 1H), 5.45 (t, 1H, J = 5.7 Hz), 3.85−3.76 (m, 1H), 2.08−2.01 (m, 2H), 1.94−1.79 (m, 2H), 1.72−1.58 (m, 2H), 1.39−1.09 (m, 6H), 1.01 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 169.4, 166.1, 145.1, 140.4, 134.9, 111.7, 78.6, 48.3, 33.5, 33.3, 25.8, 25.7, 25.2, 25.1, 9.5; MS (DI, CI NH_3) *m*/*z* 308; IR (thin film) 2932, 1654, 1603, 1519, 1469, 1346 cm^{-1}; HRMS calcd for $C_{15}H_{21}N_3O_4$307.1532, found 307.1528; mp 158 °C.

***N*-Cyclohexyl-2-(2,6-dimethylpyrimidin-4-yloxy)butyramide (Table 7, entry 4):** yellow solid; yield 60%; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.47 (s, 1H), 6.05 (br s, 1H), 5.41 (dd,1H, J = 6.6, 4.8 Hz), 3.83−3.72 (m, 1H), 2.53 (s, 3H), 2.41 (s, 3H), 2.03−1.94 (m, 2H), 1.70−1.53 (m, 4H), 1.37−1.29 (m, 2H), 1.20−1.02 (m, 4H), 0.95 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 169.9, 168.8, 168.4, 168.0, 104.0, 76.9, 48.1, 33.5, 33.3, 26.2, 25.8, 25.6, 25.1, 24.3, 9.5; MS (DI, CI NH_3) *m*/*z* 292; IR (thin film) 2360, 1591, 1560 cm^{-1}; MS (DI, CI NH_3) *m*/*z* 292; HRMS calcd for $C_{16}H_{25}N_3O_2$ 291.1947, found 291.1939; mp 85 °C.

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Supporting Information Available: Experimental procedures and characterization data for all other new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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