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# Multicomponent Reactions of Convertible Isonitriles

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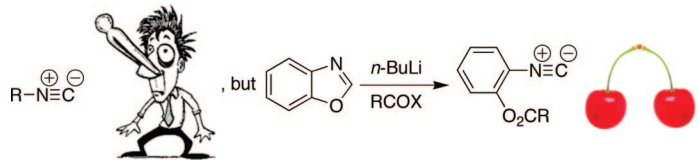


A new family of unsaturated isonitriles has been prepared by the base-promoted ring-opening of oxazoles, offering an alternative to the conventional formamide dehydration route. These compounds undergo the full complement of multicomponent reactions for which isonitriles are known and offer the desirable trait of giving amide products that readily participate in acyl substitution reactions (hence, they are convertible). Moreover, they do not have the objectionable odors for which isonitriles are typically known, making them more accessible as reagents for organic synthesis. One focus of the work is isonitriles bearing perfluorinated alkyl groups that enable the ready separation of such reagents from nonfluorinated reaction products using the "light" fluorous method of fluorous solid-phase extraction.



## Introduction

Isonitriles are versatile functional groups owing to their status as the longest-known stable divalent carbon derivatives. The reactions in which they participate are quite varied, including free radical additions,[1] organometallic transformations like the Pauson-Khand reaction,[2] and polymerizations.[3] Isonitriles have also been quite prolific in multicomponent reactions.[4] The attractions of these functional groups are offset by several disadvantages. Few isonitriles are available from major commercial suppliers, likely for reasons to follow. They are typically not simple to prepare, the best method being based on the dehydration of formamides with the dangerous reagent phosgene.[5] While some alternative syntheses have been reported,[6] they are typically not as general. Isonitriles also convey quite offensive odors. Ugi admits "The development of the chemistry of isonitriles has probably suffered through the characteristic odor of volatile isonitriles, which has been described by Hofmann and Gautier as 'highly specific, almost overpowering', 'horrible', and 'extremely distressing'". A qualitative test for primary amines (sometimes called the carbylamine test) is based on the Hofmann reaction with dichlorocarbene, which leads to formation of an isonitrile whose presence is detected by its foul odor.[7] To quote odor theorist Luca Turin, "isonitriles" are just the Godzilla of smells, you can't believe how awful they smell, they make you vomit your guts out instantly."[8] This property has even prompted the inclusion of isonitriles in nonlethal weaponry.[9]

We were attracted by a little-used route to isonitriles based on the base-promoted ring-opening of heterocycles such as benzoxazoles or oxazoles to give *O*-acylated products like **3** (Scheme 1).[10] This method has seen use in the preparation of ortho oxygen-substituted aryl isonitriles used as ligands for metal complexes.[11] This ring-opening process has been closely studied mechanistically, and NMR spectra have been observed of α-isocyanoenolates (**2**) and *o*-isocyanophenolates with several counterions.[12] The reactions of the α-isocyanoenolates are complicated by their ambident nature. The simple system **2** eventually gives a ring-closed product **5** upon silylation, but

(1) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177.
(2) Dixon, S.; Whitby R. J. In *Titanium and Zirconium in Organic Synthesis*; Wiley-VCH: Wienheim, 2003.
(3) Drenth, W.; Nolte, R. J. M. *Acc. Chem. Res.* **1979**, *12*, 30.
(4) (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (b) Zhu, J.; Bienaymé, H. *Multicomponent Reactions*; Wiley-VCH: Wienheim, 2005. (c) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (d) Akritopoulou-Zanze, I. *Curr. Opin. Chem. Biol.* **2008**, *12*, 324.
(5) Ugi, I.; Fetzer, U.; Eholzer, U.; Knupfer, H.; Offermann, K. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 472.
(6) Atkinson, R. S.; Harger, M. J. P. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2619.
(7) (a) Hofmann, A. W. *Ber. Drsch. Chem. Ges.* **1870**, *3*, 767. (b) Norris, J. F. *Experimental Organic Chemistry*; McGraw-Hill: New York, 1915; p 87.
(8) Burr, C. *The Emperor of Scent: A Story of Perfume, Obsession, and the Last Mystery of the Senses*; Random House: New York, 2002.
(9) Pinney, V. R. Malodorant compositions, related non-lethal weapon systems, and methods of their use. US Pat. 6 352 032, March 5, 2002.
(10) Whitney, S. E.; Rickborn, B. *J. Org. Chem.* **1991**, *56*, 3058.
(11) (a) Tamm, M.; Hahn, F. E. *Coord. Chem. Rev.* **1999**, *182*, 175. (b) Hahn, F. E.; Lügger, T. *J. Organomet. Chem.* **1994**, *481*, 189. (c) Kernbach, U.; Lügger, T.; Hahn, F. E.; Fehlhammer, W. P. *J. Organomet. Chem.* **1997**, *541*, 51. (d) Hahn, F. E.; Imhof, L. *Organometallics* **1997**, *16*, 763.



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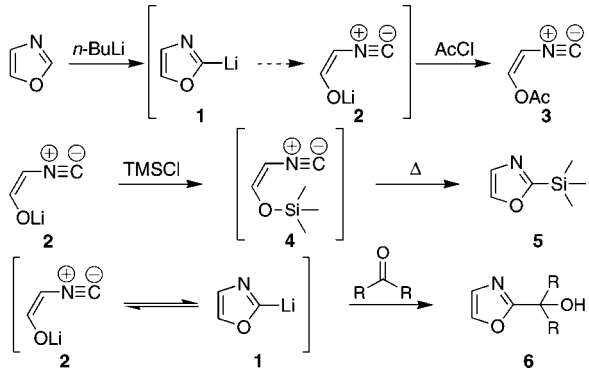
**SCHEME 1**



the *O*-silylated open chain form **4** is an intermediate.[13] Anion **2** reacts with carbonyl electrophiles in the ring-closed form to give *C*-hydroxyalkylated products **6**.[14] The C-4 iodination of lithiated oxazole is also thought to involve C-iodination of the ring-opened form **2** followed by ring closure.[15]

We viewed the base-promoted ring-opening of oxazoles as an attractive entry into functionalized, unsaturated isonitriles useful in synthesis, and aimed to develop methods to prepare these materials that would reliably trap the ambident intermediate on oxygen in the open-chain form. We then showed these compounds confer attractive reactivity on Ugi reaction products, making them a novel representative of the family of "convertible isonitriles",[16] that is, those whose Ugi reaction products are activated for acyl substitution and related processes. The process reported here was also foreshadowed by the base-promoted ring-opening of oxazolines to prepare convertible isonitriles.[16e−h] We further discovered that many of the newly prepared compounds do not exhibit the repugnant odors characteristic of many other isonitriles. These properties should encourage the use of this family of reagents in organic synthesis. Parts of this work have been reported in communication form.[17]

## Results

Initial studies focused on oxazoles. Adapting Hodges' method,[14] oxazole was treated with *n*-BuLi at −78 °C in THF, followed by addition of an acylating agent and warming to room temperature for 2 h. Compound **3** was obtained in >80% yield using this method, as was derivative **7** that incorporates an *O*-formyl mandelate as a potential chiral auxiliary. In these reactions of metalated oxazole with acetyl and *O*-formyl mandeloyl chlorides, no trace could be found of *C*-acylation to give the closed-chain form. Attempts to extend this chemistry to another commercially available oxazole gave poor results.

**SCHEME 2**

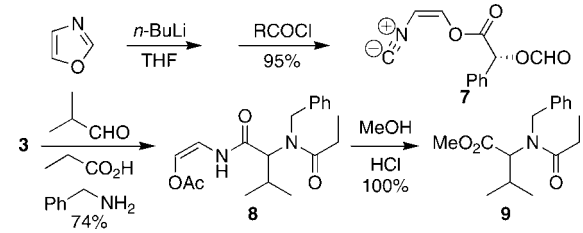
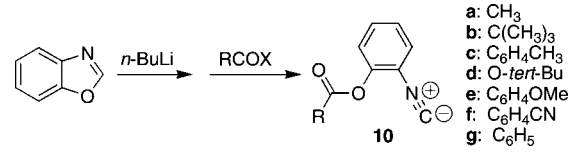
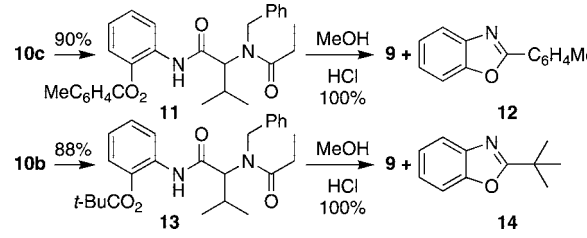


**TABLE 1. Preparation of Aromatic Isonitrile-Esters**



| compound **10** | acylating agent | yield of isonitrile | odor |
|---|---|---|---|
| **a** | AcCl | 85% | malt |
| **b** | PivCl | 92% | natural rubber |
| **c** | $MeC_6H_4COCl$ | 96% | creosote |
| **d** | $Boc_2O$ | 83% | taffy |
| **e** | $MeOC_6H_4COCl$ | 96% | mild cherry |
| **f** | $NCC_6H_4COCl$ | 90% | old wood |
| **g** | $C_6H_5COCl$ | 93% | mild petroleum |
| **h** | $C_8F_{17}C_6H_4COCl$ | 93% | odorless |

**SCHEME 3**



Under the same reaction conditions, 5-phenyloxazole reacts with either menthyl chloroformate or *O*-formyl mandeloyl chloride to give closed-chain, C2-acylated oxazole products (not shown), as evidenced by the lack of an isonitrile stretch in their IR spectra.

An Ugi reaction of **3** in methanol gives product **8** in 74% yield (Scheme 2). Compound **7** could be successfully used in a similar Ugi reaction, but it provided no diastereoselectivity. As an enamide, **8** resembles the *N*-cyclohexenyl amides used by Armstrong for the conversion of Ugi reaction products to other acyl derivatives. We therefore examined reactions of **8** under Armstrong's conditions, anhydrous HCl in methanol at 55 °C for 3 h. Methyl ester **9** was obtained in quantitative yield.

We then investigated conversion of benzoxazole to the corresponding isonitrile by trapping of the ring-opened phenolate intermediate. Under similar conditions, using *n*-BuLi at low temperature in THF followed by addition of acid chlorides or anhydrides and warming to room temperature, a variety of *ortho*-substituted phenylisonitrile derivatives **10** were obtained. The results are summarized in Table 1.

The conversion reaction of a simple Ugi product **11** derived from isonitrile **10c** in 90% yield was examined under the same conditions used with **8**, and **9** was obtained in quantitative yield (Scheme 3). For the conversion reaction of **8**, a product derived from the enamide fragment could not be isolated/identified (but it is presumably an aminoacetaldehyde derivative). With Ugi product **11**, the greater mass of the isonitrile-derived portion of

(12) Bayh, O.; Awad, H.; Mongin, F.; Hoarau, C.; Bischoff, L.; Trécourt, F.; Quéguiner, G.; Marsais, F.; Blanco, F.; Abarca, B.; Ballesteros, R. *J. Org. Chem.* **2005**, *70*, 5190.

(13) Dondoni, A.; Dall'Occo, T.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Chem. Soc., Chem. Commun.* **1984**, 258.

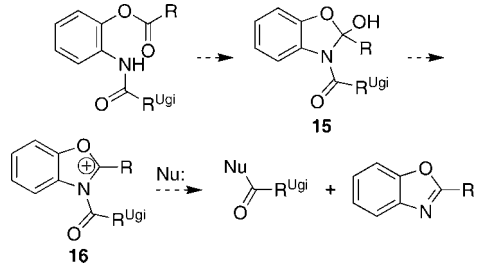
(14) Hodges, J. C.; Patt, W. C.; Connolly, C. J. *J. Org. Chem.* **1991**, *56*, 449.

(15) Vedejs, E.; Luchetta, L. M. *J. Org. Chem.* **1999**, *64*, 1011.

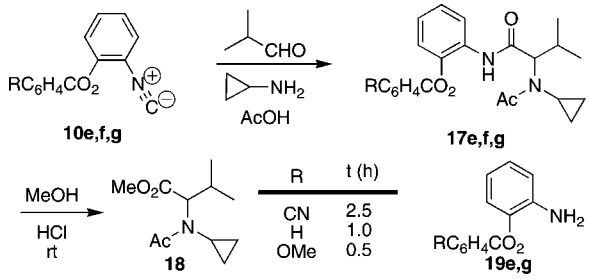
(16) (a) Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1995**, *117*, 7842. (b) Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 2574. (c) Gilley, C. B.; Buller, M. J.; Kobayashi, Y. *Org. Lett.* **2007**, *9*, 3631. (d) Gilley, C. B.; Kobayashi, Y. *J. Org. Chem.* **2008**, *73*, 4198. (e) Lindhorst, T.; Bock, H.; Ugi, I. *Tetrahedron* **1999**, *55*, 7411. (f) Linderman, R. J.; Binet, S.; Petrich, S. R. *J. Org. Chem.* **1999**, *64*, 336. (g) Kennedy, A. L.; Fryer, A. M.; Josey, J. A. *Org. Lett.* **2002**, *4*, 1167. (h) Rikimaru, K.; Yanagisawa, A.; Kan, T.; Fukuyama, T. A. *Synlett* **2004**, 41. (i) Kreye, O.; Westermann, B.; Wessjohann, L. A. *Synlett* **2007**, 3188.

(17) Pirrung, M. C.; Ghorai, S. *J. Am. Chem. Soc.* **2006**, *128*, 11772.

**SCHEME 4**



**SCHEME 5**



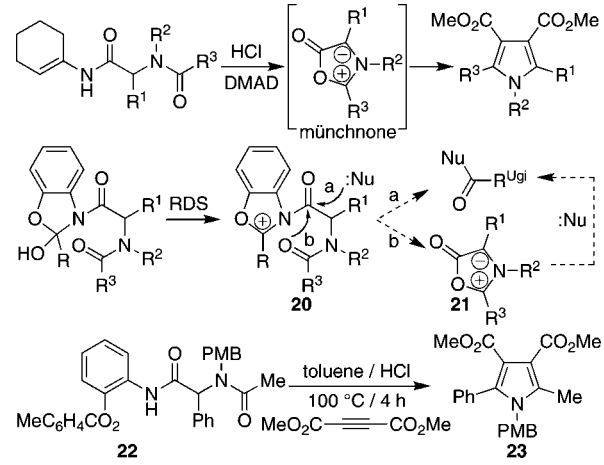
the molecule was expected to allow the other conversion product to be isolated. This other product proved to be aryl benzoxazole **12**. A similar Ugi product **13** was prepared from isonitrile **10b**, and its conversion to the methyl ester **9** using Armstrong's conditions was accompanied by the formation of **14**.

We considered several possible mechanisms for this acyl substitution process; one is delineated above (Scheme 4). Cyclization of the amide nitrogen onto the ester gives the tetrahedral intermediate **15**. Upon OH protonation and loss of water, a stabilized cation **16** could be formed that should be a quite reactive acylating agent. Nucleophilic acyl substitution would give the Ugi conversion product and the observed benzoxazole.

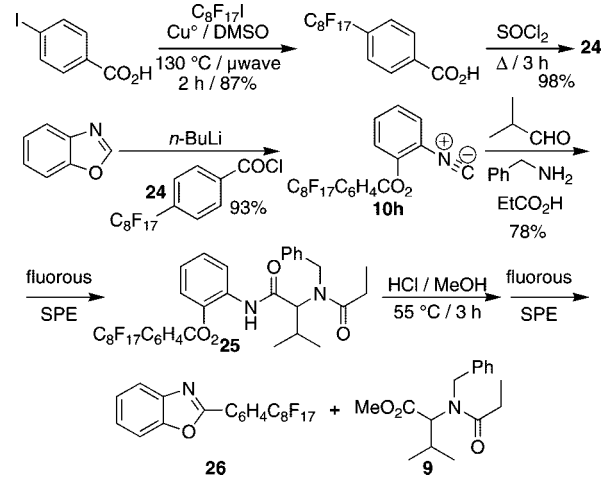
To further probe this mechanism and perhaps provide evidence concerning the rate-limiting step of the process, we examined the effect of aromatic substitution on the conversion. The initial cyclization step would presumably be faster with a more electron-deficient ester carbonyl group (engendered by an electron-withdrawing R substituent), whereas an electron-donating R substituent should promote either the protonation of the ester carbonyl or the ionization step to cation **16**. Isonitriles **10e**, **10f**, and **10g** provide a means to examine this question. They were used in standard Ugi reactions to give products **17**, which were subjected to the conversion reaction with HCl/MeOH. Notably, all of these reactions occur readily at room temperature, rather than the 55 °C used for cyclohexenamides. The time for the reaction to reach completion at room temperature is dependent on the aromatic substituent, with the electron-rich benzoate giving **18** fastest. These results support the mechanistic pathway in Scheme 4 and suggest that the rate-determining step is formation of the cation **16**. However, an anomalous observation that confuses the issue is that rather than **17e** and **17g** giving the benzoxazoles, the open-chain aniline-esters **19** were obtained.

There are further questions to be answered about the mechanism of the acyl substitution step. Armstrong implicated oxazolone (or münchnone) intermediates (Scheme 6) in the acyl substitution of cyclohexenamide Ugi products by trapping them in dipolar cycloaddition reactions (when the $R^1$ substituent is aromatic) to give pyrroles.[16b] We therefore considered the involvement of

**SCHEME 6**



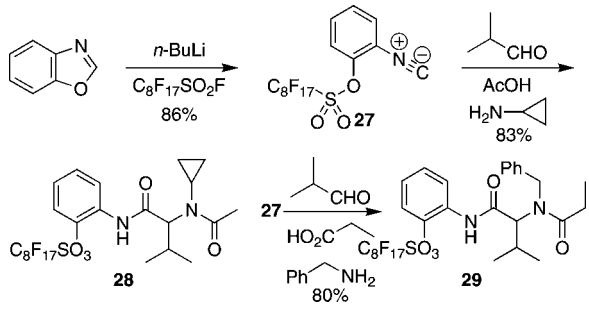
**SCHEME 7**



münchnones in the conversion reactions under study here. Two pathways of acyl substitution are possible following the generation of **20**. One involves direct reaction with a nucleophile (path a), and the other proceeds via the intermediacy of **21**, formed by an intramolecular nucleophilic substitution that should compete effectively with intermolecular processes (path b). Evidence on the pathway followed was gained by treatment of Ugi product **22** under Armstrong's dipolar cycloaddition conditions. Pyrrole **23** was obtained in 59% yield, essentially the same outcome observed when Armstrong prepared this pyrrole from the corresponding cyclohexenamide Ugi product. Naturally, benzoxazole **12** is also formed (72% isolated yield). This result shows that generation of a münchnone from *o*-(acyloxy)phenylisonitrile Ugi reaction products is possible, and that this pathway may be followed in conversion reactions. These mechanistic views do not bear on the conversion of the products of oxazole-derived isonitriles (such as **8**), because they have a readily available mechanism for cis−trans isomerization, which would preclude reforming the oxazole.

One drawback of the conversion reaction is that it requires chromatographic separation of the desired acyl substitution product from the benzoxazole. To make this process more convenient, a "light" fluorous convertible isonitrile was prepared. The fluorous acid chloride **24** required was prepared by a known route from *p*-iodobenzoic acid.[18] The initial coupling step was significantly improved by using microwave heating, which gives *p*-perfluorooctylbenzoic acid in 87% yield in 2 h compared to the reported 44% yield in 16 h with conventional heating.

**SCHEME 8**




Benzoxazole was metalated as before and acylated with **24**, giving **10h** in excellent yield. It can be used in a fluorous Ugi process based on earlier work from the Pittsburgh group,[19] modified for "light" fluorous technology using fluorous solid-phase extraction (SPE).[20] The isonitrile **10h** is used as the limiting reagent, and the other reagents used in excess are readily removed following the reaction. They flow through fluorous silica gel when it is eluted with MeOH/$H_2O$, whereas product **25** is retained and then eluted with THF. Compound **25** was subjected to the conversion process under Armstrong's conditions. Ester **9** is eluted in 98% yield with MeOH/$H_2O$, and the benzoxazole **26** is eluted in 97% yield with THF.

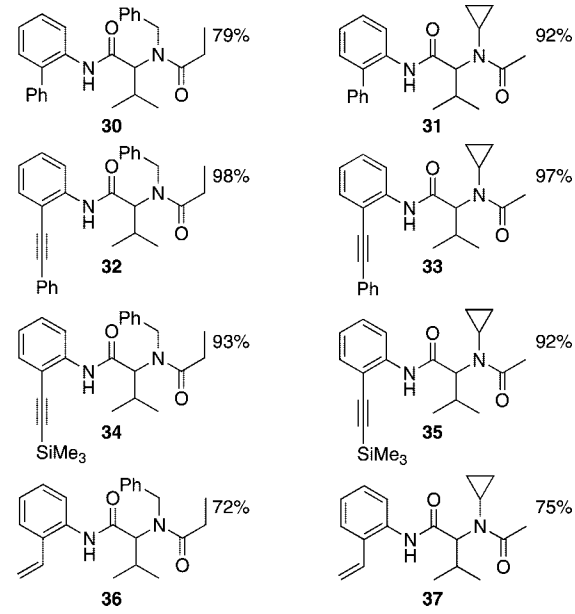
A different application of fluorous technology was investigated to elaborate the Ugi reaction products of these functionalized phenylisonitriles. Benzoxazole was metalated and the resulting phenolate was sulfonylated with a light fluorous sulfonyl halide, giving **27** (Scheme 8). This isonitrile was used in two example Ugi reactions, and the resulting products **28** and **29** were again readily purified by fluorous SPE. These compounds participate in conventional organometallic transformations such as the Suzuki (**30**−**31**), Sonogashira (**32**−**35**), and Stille (**36**−**37**) coupling reactions, as fluorous aryl sulfonates have reactivity similar to triflates,[21] giving an array of products (Chart 1) in overall excellent yields. The ability to separate these products from **28** and **29** by fluorous SPE significantly eases the cleanup of these reactions.

Few limitations to the known chemistry of isonitriles have been discerned in the reactions of compounds **10**. For example, **10b** and **10d** undergo straightforward Ugi reactions with thiocarboxylic acids to give thioamides **38**−**40** (Scheme 9).

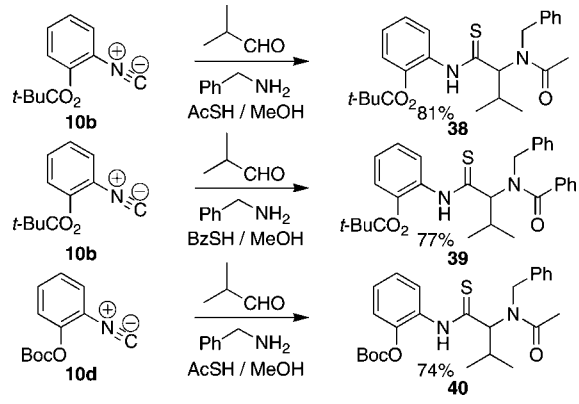
It did not prove possible to use **10a** in Ugi reactions because its aryl acetate competitively acylates the amine. However, other isonitriles in this family readily give Passerini, Gröbcke,[22] and Ugi-Smiles[23] reaction products **41**−**43**, respectively (Scheme 10).

We have been interested in the synthesis of a peptide that includes a *C*-terminal cyclobutane amino acid based on Ugi

**CHART 1**




**SCHEME 9**

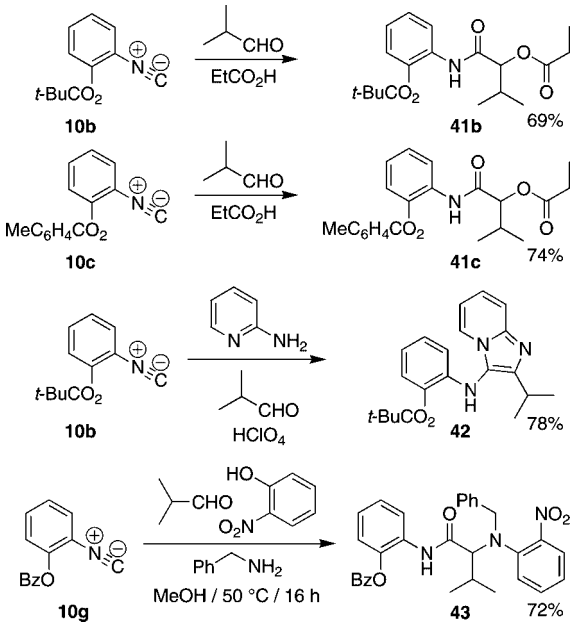



reactions of cyclobutanone.[24] For that purpose, we investigated a model reaction of convertible isonitrile **10c**, which unfortunately gives a low conversion to **44**. As an alternative, we examined the corresponding reaction with isocyanocyclohexene, which gives a far better outcome (Scheme 11). Aiming to exploit some of our recent results on the aqueous acceleration of Ugi reactions,[25] a similar reaction was investigated in water using convertible isonitrile **10b**, but no reaction was observed. Likewise, isocyanocyclohexene could be used in an Ugi reaction with a protected aspartic acid derivative to give **46** in moderate yield, but when **10b** was used instead, the yield was only 16%. These results suggest that isocyanocyclohexene is more reactive than these *o*-(acyloxy)phenylisonitriles. Scant data is available on the relative nucleophilicity of isonitriles, with only a recent report on a few isonitriles, none of them convertible.[26]

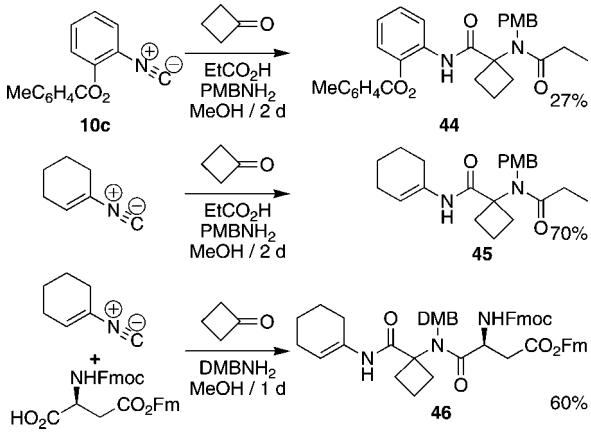
The acyloxy group in these isonitrile derivatives can offer several benefits such as facilitating the conversion reaction and permitting fluorous purification. Its asymmetric induction was also explored. For example, isonitrile **47** bearing a menthyl

(18) Paciorek, K. J. L.; Masuda, S. R.; Shih, J. G.; Nakahara, J. H. *J. Fluorine Chem.* **1991**, *53*, 233.
(19) Studer, A.; Jeger, P.; Wipf, P.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 2917.
(20) (a) Zhang, Q.; Luo, Z.; Curran, D. P. *J. Org. Chem.* **2000**, *65*, 8866. (b) Curran, D. P. *Synlett* **2001**, 1488. (c) Matsugi, M.; Curran, D. P. *Org. Lett.* **2004**, *6*, 2717.
(21) (a) Lu, Y.; Zhang, W. *QSAR Comb. Sci.* **2004**, *23*, 827. (b) Zhang, W.; Nagashima, T.; Lu, Y.; Chen, C. H-T. *Tetrahedron Lett.* **2004**, *45*, 4611. (c) Zhang, W.; Chen, C. H.-T.; Lu, Y.; Nagashima, T. *Org. Lett.* **2004**, *6*, 1473. (d) Zhang, W.; Chen, C. H.-T. *Tetrahedron Lett.* **2005**, *46*, 1807. (e) Zhang, W.; Nagashima, T. *J. Fluorine Chem.* **2006**, *127*, 588.
(22) (a) Gröbcke, K.; Weber, L.; Mehlin, F. *Synlett* **1998**, 661. (b) Lu, Y.; Zhang, W. *QSAR Comb. Sci.* **2004**, *23*, 827.
(23) El Kaïm, L.; Gizolme, M.; Grimaud, L.; Oble, J. *Org. Lett.* **2006**, *8*, 4019.
(24) (a) Wang, J. PhD Thesis, Duke University, 2007. (b) Pirrung, M. C.; Wang, J. *J. Org. Chem.* **2009**, *74*, 2958.
(25) Pirrung, M. C.; Das Sarma, K.; Wang, J. *J. Org. Chem.* **2008**, *73*, 8723.
(26) Tumanov, V. V.; Tishkov, A. A.; Mayr, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 3563.

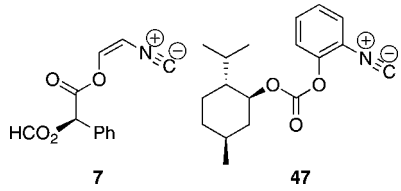
**SCHEME 10**




**SCHEME 11**




carbonate chiral auxiliary was prepared using the conventional route, and **7** was available as described earlier. However, their multicomponent reactions were completely nondiastereoselective, giving 1:1 mixtures. Evidently, conformational flexibility and the distance between the stereogenic carbon in the auxiliary and the isonitrile carbon are too great for effective asymmetric induction.




Having worked with isonitriles for some time, we quickly realized that members of this family do not exhibit the usual offensive odors to which we were accustomed. We aimed to classify their odors, and did so by an empirical jury protocol. Samples of each compound were spotted onto tissues, and all members of the laboratory were asked to smell each of them and provide a subjective description. The consensus that emerged from these organoleptic measures is included in the final column in Table 1.

## Discussion

The factors that control whether the ambident anion derived from metalating oxazoles is acylated in the open-chain or closed-chain form are not fully understood. Examples from the literature favor acylation in the closed-chain form by converting the initial lithium reagents to less electropositive metals,[27] but there are no systematic means known to favor the *O*-acylation product. The influence of oxazole substituents (e.g., 5-phenyl vs 5-H) on the acylation site is also inscrutable.

Investigations of the mechanism of the conversion process produced a dilemma. All observations suggested that the conversion involves the formation of an intermediate **16**, its cyclization to a münchnone, and its reaction with a nucleophile, until **19e** and **19g** were isolated as the byproduct of conversion reactions. It is very difficult to understand the dependence of the reaction on the aromatic substituent without the intermediacy of a species like **20**, and yet its ring must be opened to give the observed products **19**.

The ease of the conduct of Ugi reactions with these isonitriles and the subsequent reactions of the Ugi products (both acyl substitution/conversion reactions and organometallic couplings) was significantly facilitated by the use of light fluorous technology. The solid-phase extraction method for product purification/separation is less of a chromatography and more of a filtration, with no question about the separability of desired targets from other reagents.

These isonitriles have a few limitations that should be not be overlooked. They do not seem as reactive as some other isonitriles, convertible or not. We were also disappointed by our inability to use chiral versions that were readily preparable from conventional chiral auxiliaries to promote asymmetric multicomponent reactions, processes considered the final frontier in this field.[28]

## Conclusion

A novel family of convertible isonitriles has been prepared and examined in a number of the classical multicomponent reactions. The preparation of related reagents along similar lines should be a straightforward extension of this methodology, and all of these reagents should be applicable to other isonitrile-based multicomponent reactions (including newer versions such as the Passerini-Smiles, etc.). Considering the role played by isonitriles as acyl anion equivalents in the Ugi reaction, simple and mild methods such as this one to convert the products to other carboxylic acid derivatives will broaden the structural diversity of end-products accessible via multicomponent processes. The ability to work with these reagents without the accompanying pungent aroma around the lab, in the equipment, and on the researcher should also encourage their use. This virtue may apply particularly to polymer and radical chemistry, where the advantages of the conversion reaction may not be as significant. The fluorous properties of select members of the family can also be exploited more broadly.

(27) Pippel, D. J.; Mapes, C. M.; Mani, N. S. *J. Org. Chem.* **2007**, *72*, 5828.
(28) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602.

## Experimental Section

Experimental descriptions for compounds **7**−**9**, **10a**−**g**, **11**, **17**, **18**, **22**, **41b**, and **42** are available in the Supporting Information for our communication on this work.[17]

**2-Isocyanophenyl 4-Perfluorooctylbenzoate (10h).** A 50 mL round-bottom flask equipped with a magnetic stir bar and charged with benzoxazole (0.900 g, 7.56 mmol) and THF (18 mL) are allowed to cool to −78 °C for 5 min prior to addition of *n*-BuLi (1.6 M solution in hexanes, 4.96 mL, 7.94 mmol). The reaction mixture was allowed to stir at the same temperature for 1.5 h. The acid chloride **24**[29] (4.44 g, 7.94 mmol) was dissolved in 4 mL THF and added dropwise to the solution. The solution was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was poured onto a mixture of ether (100 mL) and saturated aqueous $NaHCO_3$ (50 mL). The organic layer was washed with water (2 × 50 mL), dried, and concentrated in vacuo. The resulting residue was purified by silica gel flash column chromatography and the organics concentrated in vacuo to provide the title compound (4.51 g, 93%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.39 (d, $J$ = 8.1 Hz, 2H), 7.79 (d, $J$ = 8.4 Hz, 2H), 7.50 (t, $J$ = 7.5 Hz, 2H), 7.42−7.32 (m, 2H). $^{19}$F NMR (282 MHz, $CDCl_3$): $\delta$ −81.3, −111.7, −111.8, −121.6, −122.1, −122.3, −123.1, −126.6. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 169.9, 163.0, 146.4, 134.5 (t, $J_{C-F}$ = 24.0 Hz), 132.1, 130.8, 130.7, 127.9, 127.7 (t, $J_{C-F}$ = 6.0 Hz), 127.1, 123.6, 120.4, 119.3−106.8 (m, $C_8F_{17}$). IR (film): 2124, 1748, 1490, 1454, 1413, 1371, 1332, 1298, 1262, 1198, 1143, 1115, 1104, 1093, 1068, 1048, 1017 cm$^{-1}$. MS (CI): *m*/*z* 659 (M + $NH_4$), 523. HRMS (ESI): Calcd. for $C_{22}H_9F_{17}NO_2$ $[MH]^+$, 642.0356; Found, 642.0351.

**2-(2-(*N*-Benzylpropionamido)-3-methylbutanamido)phenyl Pivalate (13).** To a solution of benzylamine (0.11 mL, 1.00 mmol) in methanol (2.0 mL) was added isobutyraldehyde (0.091 mL, 1.00 mmol), and the reaction mixture was stirred at room temperature for 10 min. To this solution was added propionic acid (0.075 mL, 1.00 mmol), and the reaction mixture was stirred for 5 min, then 2-isocyanophenyl pivalate (**10b**) (0.203 g, 1.00 mmol) was added. The resulting mixture was stirred at room temperature for 18 h and after that resulting solution was concentrated *in vacuo*. The resulting residue was purified by flash column chromatography on silica gel, eluting with $CH_2Cl_2$ to 11:1 $CH_2Cl_2$/methanol gradient to provide the title compound **13** (0.385 g, 88%) as a colorless liquid. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.47 (br s, 1H), 7.99 (dd, $J$ = 7.2, 1.8 Hz, 1H), 7.22−7.02 (m, 8H), 4.62 (s, 2H), 4.57 (d, $J$ = 11.1 Hz, 1H), 2.59−2.51 (m, 1H), 2.43−2.20 (m, 2H), 1.47 (s, 9H), 1.09 (t, $J$ = 6.9 Hz, 3H), 1.00 (d, $J$ = 6.6 Hz, 3H), 0.88 (d, $J$ = 6.6 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 176.9, 176.7, 168.7, 140.7, 137.1, 130.5, 129.0, 127.5, 126.3, 126.2, 124.4, 122.1, 66.7, 53.7, 49.5, 39.7, 27.5, 27.4, 26.6, 20.2, 19.1, 9.8; IR (film): 3190, 2970, 2875, 1757, 1696, 1635, 1607, 1526, 1479, 1451, 1414, 1369, 1309, 1275, 1251, 1230, 1180, 1097, 1028 cm$^{-1}$. MS (FAB): *m*/*z* 439 (M + H), 246. HRMS: Calcd. for $C_{26}H_{35}N_2O_4$ $[MH]^+$, 439.2597; Found, 439.2602.

**Conversion Reactions.** The procedure for compounds **11** and **13** was as follows. To a solution of Ugi product (0.3 mmol) in methanol (2.5 mL) was added acetyl chloride (1.5 mmol) in one portion. The flask was equipped with a reflux condenser and heated to 55 °C for 3 h. The reaction was cooled to room temperature and the solvent was removed *in vacuo*. The resulting residue was purified by flash column chromatography on silica gel, eluting with hexanes to 19:1 hexanes/ethyl acetate gradient to provide ester **9** as a colorless liquid. The other products were: 2-*p*-tolylbenzo[*d*]oxazole (**12**), a known compound[30] that exhibits spectral properties consistent with this structure, and 2-*tert*-butylbenzo[*d*]oxazole (**14**), a known compound[31] that exhibits spectral properties consistent with this structure. The standard procedure for compounds **18** was as follows. To a solution of Ugi product (0.06 mmol) in methanol (0.1 mL) was added a solution of acetyl chloride (0.3 mmol) in methanol (0.5 mL) in one portion. The resulting solution was stirred at room temperature until the starting material disappeared. The solvent was removed *in vacuo* and purified by flash column chromatography on silica gel, eluting with hexanes to 7:3 hexanes/ethyl acetate gradient to provide the methyl ester **18** as a colorless liquid. When **17g** was used the reactant, ester **18** was produced in quantitative yield and 2-aminophenyl benzoate (**19g**) was produced in 95% yield. It gave spectral properties identical to the known compound.[32] When **17e** was used as a reactant, the ester **18** was produced in quantitative yield and 2-aminophenyl 4-methoxybenzoate (**19e**) was produced in 94% yield. It gave spectral properties identical to the known compound.[33]

**Dimethyl 1-(4-methoxybenzyl)-2-methyl-5-phenyl-1H-pyrrole-3,4-dicarboxylate (23).** The amide **22** (0.052 g, 0.10 mmol) was azeotropically dried with toluene, and then dissolved in toluene (2 mL). The dimethyl acetylenedicarboxylate (0.062 mL, 0.50 mmol) was added to the reaction mixture followed by HCl (1.0 M solution in anhydrous ether, 0.3 mL, 0.30 mmol). The flask was then capped and heated at 100 °C for 4 h. After cooling the reaction mixture solvent was evaporated and the residue was taken up in $CH_2Cl_2$ and filtered. The soluble portion was purified by flash column chromatography on silica gel, eluting with $CH_2Cl_2$ to 19:1 $CH_2Cl_2$/methanol gradient to provide the title compound **23** (0.023 g, 59%) as a white solid. This compound is known from Armstrong's work and our product showed identical spectral properties.[16]

***p*-Perfluorooctylbenzoic Acid.** To a solution of 4-iodobenzoic acid (0.248 g, 1.00 mmol) and perfluorooctyl iodide (0.29 mL, 1.10 mmol) in DMSO (2.5 mL) was added Cu powder (0.191 g, 3.00 mmol). The reaction mixture and a magnetic stir bar were sealed in the reaction vessel of a Discover monomode microwave apparatus (CEM) and irradiated for 2 h at 130 °C. Temperature was monitored with the IR temperature monitoring feature of the Discover reactor. After cooling to room temperature, $CH_2Cl_2$ was added to the reaction mixture and the inorganic salts were filtered and washed with more $CH_2Cl_2$. The combined solution was then washed with water, dried and concentrated *in vacuo*. The crude product was purified by crystallization from ethanol gives the title compound (0.47 g, 87%) as a white solid. This compound is known and the properties of this material were consistent with that report.[18]

**General Procedure for Fluorous Ugi Reactions.** To a solution of amine (1.0 mmol) in methanol (2.0 mL) was added aldehyde (1.0 mmol), and the reaction mixture was stirred at room temperature for 10 min. To this solution was added carboxylic acid (1.0 mmol), and the reaction mixture was stirred for 5 min, and isonitrile (1.0 mmol) was added. The resulting mixture was stirred at room temperature until the reaction was determined to be complete by TLC. The resulting solution was concentrated in vacuo and purified by fluoroflash silica gel flash column chromatography (solvents noted) to provide the title compounds.

**2-(2-(*N*-benzylpropionamido)-3-methylbutanamido)phenyl 4-Perfluorooctylbenzoate (25).** Prepared according to the general procedure for 15 h to provide title compound as a colorless liquid (78%) after purification by flash column chromatography on fluoroflash silica gel, eluting with 80% MeOH/$H_2O$ followed by THF. The title compound exists as a two rotamers in 4:1 ratio at room temperature in chloroform. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 9.63 (br s, 0.2H), 9.38 (br s, 0.8H), 8.45 (d, $J$ = 8.4 Hz, 1.6H),

(29) Matsui, M.; Tanka, N.; Nakaya, K.; Funabiki, K.; Shibata, K.; Muramatsu, H.; Abe, Y.; Kaneko, M. *Liq. Cryst.* **1997**, *23*, 217.

(30) (a) Kawashita, Y.; Nakamichi, N.; Kawabata, H.; Hayashi, M. *Org. Lett.* **2003**, *5*, 3713. (b) Derridj, F.; Djebbar, S.; Benali-Baitich, O.; Doucet, H. *J. Organomet. Chem.* **2008**, *693*, 135.

(31) (a) Tauer, E.; Grellmann, K. H. *J. Org. Chem.* **1981**, *46*, 4252. (b) DeLuca, M. R.; Kerwin, S. M. *Tetrahedron* **1997**, *53*, 457. (c) Yoshida, Y.; Hamada, Y.; Umezu, K.; Tabuchi, F. *Org. Proc. Res. Dev.* **2004**, *8*, 958. (d) Altenhoff, G.; Glorius, F. *Adv. Synth. Cat.* **2004**, *346*, 1661.

(32) (a) So, Y.-H.; Heeschen, J. P. *J. Org. Chem.* **1997**, *62*, 3552. (c) Marshall, F. J.; Sigal, M. V., Jr.; Sullivan, H. R.; Cesnik, C.; Root, M. A. *J. Med. Chem.* **1963**, *6*, 60.

(33) Jan, T.; Floner, D.; Moinet, C. *Electrochim. Acta* **1997**, *42*, 2073.

8.38 (d, $J = 8.4$ Hz, 0.4H), 8.24 (d, $J = 8.1$ Hz, 0.2H), 8.19 (d, $J = 8.1$ Hz, 0.8H), 7.78 (d, $J = 8.4$ Hz, 1.6H), 7.66 (d, $J = 8.4$ Hz, 0.4H), 7.43 (d, $J = 8.1$ Hz, 0.4H), 7.30−7.05 (m, 7.2H), 6.85 (d, $J = 6.3$ Hz, 0.4H), 4.54 (d, $J = 15.6$ Hz, 0.2H), 4.53 (s, 1.6H), 4.41 (d, $J = 15.6$ Hz, 0.2H), 4.16 (br m, 1H), 2.86−2.73 (m, 0.2H), 2.65−2.53 (m, 0.8H), 2.25−2.01 (m, 2H), 1.06 (d, $J = 6.3$ Hz, 0.6H), 1.03 (d, $J = 6.3$ Hz, 0.6H), 0.97 (d, $J = 6.3$ Hz, 2.4H), 0.80 (d, $J = 6.3$ Hz, 2.4H), 0.71 (t, $J = 7.2$ Hz, 3H). $^{19}$F NMR (282 MHz, $CDCl_3$): $\delta$ −81.2, −81.3, −111.5, −111.6, −121.5, −122.1, −122.3, −123.1, −126.5. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 177.1, 173.3, 169.1, 168.5, 164.2, 164.0, 140.2, 139.6, 136.6, 135.7, 133.9 (t, $J_{C-F} = 24.0$ Hz), 132.9, 131.0, 130.0, 129.0, 128.9, 128.0, 127.8, 127.4 (t, $J_{C-F} = 6.0$ Hz), 127.2, 127.0, 126.6, 124.5, 124.4, 122.3, 122.2, 122.1, 119.3−106.8 (m, $C_8F_{17}$), 69.7, 51.0, 27.5, 26.6, 26.5, 20.2, 19.6, 19.3, 9.0. IR (film): 3266, 2971, 1747, 1693, 1630, 1610, 1533, 1498, 1454, 1413, 1369, 1238, 1199, 1146, 1105, 1068, 1030, 1018 cm$^{-1}$. MS (FAB): *m/z* 915 (M + K), 899 (M + Na). HRMS (ESI): Calcd. for $C_{36}H_{30}F_{17}N_2O_4[MH]^+$, 877.1929; Found, 877.1926.

**General Procedure for Fluorous Conversion Reactions. 2-(*p*-Perfluorooctyl)benzo[*d*]oxazole (26).** To a solution of fluorous Ugi product **25** (0.263 g, 0.3 mmol) in methanol (2.5 mL) was added acetyl chloride (0.107 mL, 1.5 mmol) in one portion. The flask was equipped with a reflux condenser and heated to 55 °C for 3 h. The reaction was cooled to room temperature and the solvent was removed *in vacuo*. The resulting residue was purified by flash column chromatography on fluoroflash silica gel, eluting with 80% MeOH/$H_2O$ to give methyl ester **9** followed by THF to give the title compound **26** (0.178 g, 97%) as a white solid. mp: 155.5−156.8 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.40 (d, $J = 8.1$ Hz, 2H), 7.83−7.80 (m, 1H), 7.77 (d, $J = 8.1$ Hz, 2H), 7.65−7.60 (m, 1H), 7.44−7.37 (m, 2H). $^{19}$F NMR (282 MHz, $CDCl_3$): $\delta$ −81.2, −111.47, −111.53, −121.5, −122.1, −122.2, −123.1, −126.5. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 161.7, 151.1, 142.2, 131.7 (t, $J_{C-F} = 24.0$ Hz), 130.9, 127.9, 127.8 (t, $J_{C-F} = 6.0$ Hz), 126.1, 125.2, 120.7, 119.3−106.8 (m, $C_8F_{17}$), 111.1. IR (film): 2927, 1609, 1558, 1506, 1473, 1455, 1416, 1371, 1334, 1299, 1196, 1143, 1111, 1093, 1059, 1046, 1017, 1002 cm$^{-1}$. MS (CI): *m/z* 631 (M + $NH_4$). Anal. Calcd. for $C_{21}H_8F_{17}NO$: C, 41.13; H, 1.31; N, 2.28; Found: C, 41.41; H, 1.68; N, 2.25. HRMS (ESI): Calcd. for $C_{21}H_9F_{17}NO[MH]^+$, 614.0407; Found, 614.0409.

**2-Isocyanophenyl Perfluorooctanesulfonate (27).** A 50 mL round-bottom flask equipped with a magnetic stir bar and charged with benzoxazole (1.00 g, 8.39 mmol) and THF (20 mL) are allowed to cool to −78 °C for 5 min prior to addition of *n*-BuLi (1.6 M solution in hexanes, 5.50 mL, 8.80 mmol). The reaction mixture was allowed to stir at the same temperature for 1.5 h. The perfluoro-1-octanesulfonyl fluoride (2.43 mL, 8.81 mmol) was added dropwise to the solution. The solution was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was poured onto a mixture of ether (100 mL) and saturated aqueous $NaHCO_3$ (50 mL). The organic layer was washed with water (2 × 50 mL), dried, and concentrated in vacuo. The resulting residue was purified by silica gel flash column chromatography eluting with hexanes to a 24:1 hexanes/ethyl acetate gradient to provide the title compound **27** (4.34 g, 86%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.57−7.51 (m, 1H), 7.50−7.42 (m, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 173.1, 144.5, 131.1, 129.3, 129.0, 122.9, 120.4, 119.2−106.8 (m, $C_8F_{17}$). $^{19}$F NMR (282 MHz, $CDCl_3$): $\delta$ −72.2, −81.1, −108.9, −119.9, −121.7, −122.0, −122.2, −123.1, −126.5. IR (film): 2127, 1489, 1433, 1371, 1332, 1198, 1150, 1096, 1062, 1037 cm$^{-1}$. MS (CI): *m/z* 619 (M + $NH_4$), 602 (M + H). Anal. Calcd. for $C_{15}H_4F_{17}NO_3S$: C, 29.97; H, 0.67; N, 2.33; Found: C, 29.94; H, 0.78; N, 2.36.

**2-(*N*-Benzylpropionamido)-*N*-(biphenyl-2-yl)-3-methylbutanamide (30).** Compound **29** (0.074 g, 0.088 mmol) was added to a flask and dissolved in 1 mL of DMF. LiCl (0.011 g, 0.26 mmol) was added followed by $Pd(PPh_3)_2Cl_2$ (3 mg, 4.4 nmol). Aqueous $Na_2CO_3$ (2M, 0.132 mL, 0.26 mmol) was added and the reaction stirred at room temperature for 5 min. Phenyl boronic acid (0.022 g, 0.177 mmol) was added and the mixture was purged with argon followed by stirring at 80 °C for 8 h. Once the reaction was complete, water was added to the reaction mixture, and it was extracted with $CH_2Cl_2$. The combined organic layers were washed with water, dried and concentrated in vacuo affording a brownish liquid, which was purified by flash column chromatography on silica gel, eluting with hexanes to 11:1 hexanes/ethyl acetate gradient afforded the title compound (0.029 g, 79%) as a colorless liquid. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.28 (br s, 1H), 7.82 (d, $J = 8.4$ Hz, 1H), 7.48−7.09 (m, 13H), 4.65 (d, $J = 17.4$ Hz, 1H), 4.52 (d, $J = 17.4$ Hz, 1H), 4.36 (d, $J = 11.1$ Hz, 1H), 2.53−2.40 (m, 1H), 2.32−2.04 (m, 1H), 0.98 (t, $J = 7.5$ Hz, 3H), 0.95 (d, $J = 6.6$ Hz, 3H), 0.80 (d, $J = 6.6$ Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 176.2, 168.9, 138.4, 137.5, 134.7, 134.0, 130.4, 129.5, 129.1, 128.9, 128.2, 128.1, 127.5, 126.5, 124.9, 122.9, 66.9, 49.6, 27.5, 26.9, 20.1, 19.1, 9.6. IR (film): 3261, 3030, 2965, 2873, 1684, 1633, 1584, 1519, 1495, 1448, 1437, 1416, 1370, 1302, 1272, 1229, 1206, 1167, 1129, 1074, 1030, 1010 cm$^{-1}$. MS (FAB): *m/z* 415 (M + H), 246. HRMS (ESI): Calcd. for $C_{27}H_{31}N_2O_2$ $[MH]^+$, 415.2380; Found, 415.2382.

**2-(*N*-Benzylpropionamido)-3-methyl-*N*-(2-(phenylethynyl)phenyl)butanamide (32).** Compound **29** (0.071 g, 0.0.085 mmol) was added to a flask and dissolved in 0.7 mL of DMF. LiCl (0.011 g, 0.26 mmol), $Pd(PPh_3)_2Cl_2$ (3 mg, 4.4 nmol), and CuI (1 mg, 5.3 nmol) were added to the flask. After 0.9 mL of $Et_3N$ was added, the mixture was stirred at room temperature for 2 min. Phenyl acetylene (0.014 mL, 0.127 mmol) was added and the reaction mixture was purged with argon followed by stirring at 80 °C for 8 h. Once complete the reaction, water was added to the reaction mixture and extracted with $CH_2Cl_2$. The combined organic layers were washed with water, dried and concentrated in vacuo affording a brownish liquid, which was purified by flash column chromatography on silica gel, eluting with hexanes to 14:1 hexanes/ethyl acetate gradient afforded the title compound (0.036 g, 98%) as a brownish liquid. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.91 (br s, 1H), 8.08 (d, $J = 9.0$ Hz, 1H), 7.81 (d, $J = 8.1$ Hz, 2H), 7.51 (d, $J = 7.5$ Hz, 1H), 7.42−7.35 (m, 3H), 7.25−7.13 (m, 6H), 7.04 (t, $J = 7.8$ Hz, 1H), 4.90 (d, $J = 10.5$ Hz, 1H), 4.64 (s, 2H), 2.63−2.46 (m, 1H), 2.44−2.31 (m, 1H), 2.27−2.14 (m, 1H), 1.06 (m, 6H), 0.90 (d, $J = 6.3$ Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 176.4, 168.8, 138.9, 137.2, 132.2, 129.4, 128.8, 128.6, 127.3, 126.2, 123.7, 122.9, 120.2, 113.1, 96.9, 84.3, 65.4, 48.7, 27.3, 26.6, 20.2, 18.9, 9.6. IR (film): 3291, 3063, 2965, 2874, 2209, 1698, 1636, 1605, 1578, 1519, 1492, 1445, 1413, 1371, 1359, 1301, 1227, 1203, 1166, 1127, 1073, 1029 cm$^{-1}$. MS (FAB): *m/z* 461 (M + Na), 439 (M + H), 246. HRMS (ESI): Calcd. for $C_{29}H_{31}N_2O_2[MH]^+$, 439.2380; Found, 439.2383.

**2-(*N*-Cyclopropylacetamido)-3-methyl-*N*-(2-((trimethylsilyl)-ethynyl)phenyl) Butanamide (35).** Prepared according to the above procedure from **28** by using trimethylsilyl acetylene (1.5 equiv) for 8 h to provide title compound as a brownish liquid (92%) after purification by flash column chromatography on silica gel, eluting with hexanes to 19:1 hexanes/ethyl acetate gradient. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 9.43 (br s, 1H), 8.30 (d, $J = 8.1$ Hz, 1H), 7.41 (dd, $J = 7.8$, 1.2 Hz, 1H), 7.27 (td, $J = 7.8$, 1.8 Hz, 1H), 6.98 (td, $J = 7.8$, 1.2 Hz, 1H), 4.15 (d, $J = 11.1$ Hz, 1H), 2.89−2.76 (m, 1H), 2.74−2.67 (m, 1H), 2.27 (s, 3H), 1.17−1.09 (m, 1H), 1.06 (d, $J = 6.3$ Hz, 3H), 0.96 (d, $J = 6.6$ Hz, 3H), 0.93−0.80 (m, 3H), 0.31 (s, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 174.7, 170.2, 140.0, 132.6, 129.6, 123.4, 120.0, 113.2, 102.2, 100.0, 71.2, 32.0, 29.9, 27.0, 23.4, 20.5, 20.0, 9.5, 0.1. IR (film): 3281, 2964, 2156, 1697, 1684, 1646, 1602, 1577, 1521, 1447, 1386, 1324, 1300, 1248, 1200, 1187, 1136, 1116, 1104, 1035 cm$^{-1}$. MS (CI): *m/z* 371 (M + H), 182. HRMS (ESI): Calcd. for $C_{21}H_{31}N_2O_2Si$ $[M]^+$, 371.2149; Found, 371.2151.

**2-(*N*-Benzylpropionamido)-3-methyl-*N*-(2-vinylphenyl)butanamide (36).** Compound **29** (0.089 g, 0.106 mmol) was added to a flask and dissolved in 0.8 mL of DMF. The tributylvinyl tin (0.038 mL, 0.128 mmol) was added followed by LiCl (0.023 g,

0.532 mmol) and $Pd(PPh_3)_2Cl_2$ (0.004 g, 0.005 mmol). The reaction mixture was purged with argon and stirred at 125 °C for 24 h. Once complete the reaction, water was added to the reaction mixture and extracted with $CH_2Cl_2$. The combined organic layers were washed with water, dried and concentrated in vacuo affording a colorless liquid, which was purified by flash column chromatography on silica gel, eluting with hexanes to 11:1 hexanes/ethyl acetate gradient afforded the title compound **36** (0.028 g, 72%) as a colorless liquid. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.84 (br s, 1H), 7.68 (d, $J$ = 8.1 Hz, 1H), 7.45 (d, $J$ = 7.8 Hz, 1H), 7.35−7.11 (m, 7H), 6.87 (dd, $J$ = 17.1, 11.1 Hz, 1H), 5.69 (d, $J$ = 17.1 Hz, 1H), 5.42 (d, $J$ = 11.1 Hz, 1H), 4.70 (d, $J$ = 17.1 Hz, 1H), 4.61 (d, $J$ = 17.1 Hz, 1H), 4.37 (d, $J$ = 9.3 Hz, 1H), 2.70−2.65 (m, 1H), 2.47−2.26 (m, 2H), 1.13 (t, $J$ = 7.2 Hz, 3H), 1.03 (d, $J$ = 6.3 Hz, 3H), 0.89 (d, $J$ = 6.3 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 177.1, 169.0, 137.0, 134.7, 132.1, 130.1, 129.0, 128.5, 127.7, 126.7, 125.2, 123.2, 117.9, 68.9. 50.8, 27.8, 27.0, 20.2, 19.4, 9.8. IR (film): 3253, 2966, 2936, 2874, 1684, 1627, 1581, 1520, 1496, 1451, 1416, 1360, 1297, 1232, 1207, 1168, 1127, 1074, 1029 cm$^{-1}$. MS (FAB): $m/z$ 387 (M + Na), 246. HRMS (ESI): Calcd. for $C_{23}H_{29}N_2O_2$ $[M]^+$, 365.2224; Found, 365.2220.

**2-(3-Methyl-2-(propionyloxy)butanamido)phenyl 4-Methylbenzoate (41c).** To a solution of 2-isocyanophenyl 4-methylbenzoate (**10c**) (0.152 g, 0.64 mmol) in $CH_2Cl_2$ (1.5 mL) were added isobutyraldehyde (0.058 mL, 0.64 mmol) followed by propionic acid (0.048 mL, 0.64 mmol), and the reaction mixture was stirred at room temperature for 18 h. After completion of the reaction, solvent was removed *in vacuo*, and the residue was purified by flash column chromatography on silica gel, eluting with hexanes to 10:1 hexanes/ethyl acetate gradient afforded the title compound **41c** (0.181 g, 74%) as a pale-yellow liquid. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.23 (d, $J$ = 8.1 Hz, 1H), 8.11 (d, $J$ = 8.1 Hz, 2H), 8.01 (br s, 1H), 7.35 (d, $J$ = 8.1 Hz, 2H), 7.33−7.16 (m, 3H), 5.22 (d, $J$ = 3.6 Hz, 1H), 2.47 (s, 3H), 2.41−2.28 (m, 1H), 2.19−1.94 (m, 2H), 0.94 (t, $J$ = 7.8 Hz, 3H), 0.92 (d, $J$ = 7.2 Hz, 3H), 0.91 (d, $J$ = 7.2 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 172.9, 167.9, 164.7, 145.5, 141.2, 130.5, 129.8, 129.6, 126.9, 126.0, 125.5, 123.1, 122.5, 77.9, 31.1, 27.4, 22.0, 18.9, 16.9, 9.1. IR (film): 3425, 2968, 1740, 1697, 1609, 1524, 1480, 1453, 1265, 1239, 1173, 1104, 1057, 1017 cm$^{-1}$. MS (FAB): $m/z$ 384 (M + H), 119. HRMS (ESI): Calcd. for $C_{22}H_{26}NO_5[MH]^+$, 384.1806; Found, 384.1811.

**2-(2-(Benzyl(2-nitrophenyl)amino)-3-methylbutanamido)phenyl Benzoate (43).** Benzylamine (0.11 mL, 1.00 mmol), *o*-nitrophenol (0.139 g, 1.00 mmol), and isobutyraldehyde (0.091 mL, 1.00 mmol) were added to a solution of 2-isocyanophenyl benzoate (**10g**) (0.223 g, 1.00 mmol) in methanol (1.0 mL). The resulting mixture was stirred at 50 °C under an inert atmosphere for 16 h and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel, eluting with hexanes to 2:1 hexanes/ethyl acetate gradient afforded the title compound **43** (0.377 g, 72%) as a colorless liquid. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.18−8.13 (m, 3H), 7.74 ≤ 7.65 (m, 2H), 0.756−7.51 (m, 2H), 7.29−7.09 (m, 10H), 6.88−6.83 (m, 1H), 4.42 (d, $J$ = 16.0 Hz, 1H), 4.41 (d, $J$ = 16.0, 1H), 3.30 (d, $J$ = 9.0 Hz), 2.43 (sextuplet, $J$ = 7.2 Hz, 1H), 1.07 (d, $J$ = 7.2 Hz, 3H), 0.90 (d, $J$ = 7.2 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 168.9, 164.6, 146.8, 141.8, 141.2, 136.8, 134.2, 132.2, 130.6, 129.7, 128.9, 128.8, 128.6, 128.5, 127.39, 126.6, 126.4, 125.2, 124.6, 124.3, 123.0, 122.7, 74.5, 52.6, 28.3, 19.5, 19.3. IR (film): 2962, 1743, 1690, 1519, 1450, 1261, 1175, 1104, 1056, 706 cm$^{-1}$. HRMS (ESI): Calcd. for $C_{31}H_{30}N_3O_5$, 524.2185; Found, 524.2189.

**2-Isocyanophenyl (1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl Carbonate (47).** A 50 mL round-bottom flask equipped with a magnetic stir bar and charged with benzoxazole (1.00 g, 8.39 mmol) and THF (20 mL) are allowed to cool to −78 °C for 5 min prior to addition of *n*-BuLi (1.6 M solution in hexanes, 5.50 mL, 8.80 mmol). The reaction mixture was allowed to stir at the same temperature for 1.5 h. The (1*S*)-(+)-menthyl chloroformate (1.87 mL, 8.81 mmol) was added dropwise to the solution. The solution was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was poured onto a mixture of ether (100 mL) and saturated aqueous $NaHCO_3$ (50 mL). The organic layer was washed with water (2 × 50 mL), dried, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel, eluting with hexanes to 32:1 hexanes/ethyl acetate gradient afforded the title compound **47** (1.97 g, 78%) as a colorless liquid. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.46−7.40 (m, 2H), 7.30−7.25 (m, 2H), 4.67 (td, $J$ = 10.5, 4.8 Hz, 1H), 2.22−2.18 (m, 1H), 2.13−2.03 (m, 1H), 1.77−1.69 (m, 2H), 1.58−1.44 (m, 2H), 1.25−1.03 (m, 2H), 0.95 (d, $J$ = 6.6 Hz, 6H), 0.91−0.88 (m, 1H), 0.85 (d, $J$ = 6.9 Hz, 3H). IR (film): 2960, 2925, 2868, 2851, 2122, 1754, 1490, 1454, 1389, 1370, 1279, 1258, 1226, 1176, 1152, 1096, 1080, 1039, 1028, 1006 cm$^{-1}$. MS (FAB): $m/z$ 302 (M + H). HRMS (ESI): Calcd. for $C_{18}H_{24}NO_3$ $[MH]^+$, 302.1756; Found, 302.1747.

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**Supporting Information Available:** $^1$H NMR spectra for **10h**, **13**, **25**−**40**, **41c**, and **43**−**47**. $^{13}$C NMR spectra for **10h**, **13**, **26**−**38**, **40**,**41c**, and **43**−**46**. Experimental procedures for the preparation of **28**, **29**, **31**, **33**, **34**, **37**−**40**, **41b**, **42**, and **44**−**46**. This material is available free of charge via the Internet at http://pubs.acs.org.

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