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A New Supported Reagent for the Parallel Synthesis of Primary and Secondary *O*-Alkyl Hydroxylamines through a Base-Catalyzed Mitsunobu Reaction

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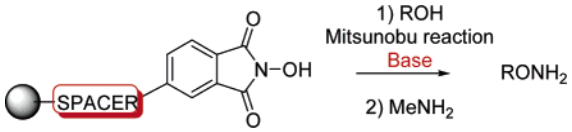

The growing field of applications of *O*-alkyl hydroxylamines in medicinal chemistry and chemical biology has motivated the search for a parallel synthesis. A solid-phase approach based on the alkylation by alcohols of a new supported *N*-hydroxyphthalimide reagent using a Mitsunobu reaction followed by methylaminolysis has been optimized. This study points out the importance of the linker and a specific base effect for the Mitsunobu reaction. A large variety of alcohols can be used to give with moderate to high yields diverse *O*-alkyl hydroxylamines in high purity.

Introduction

The *O*-alkyl hydroxylamine function is present in natural and synthetic products displaying potent pharmacological action[1] or enzyme inhibition activities.[2−4] It has motivated a medicinal interest as a non basic substitute for biologically active amines[5] or as part of bioisosteric groups.[6] More recently, it has been demonstrated that its incorporation into peptides can induce and stabilize turns or helical structures.[7] In addition, its spontaneous conversion into oxime ethers upon condensation with aldehydes and ketones, a reaction occurring with almost complete functional group compatibility, has received considerable attention. This chemoselective ligation strategy is becoming increasingly important in chemical biology,[8−11] fragment-based drug discovery,[12,13] drug targeting,[14−16] library synthesis,[17−19] and screening of asymmetric reaction catalysts.[20]

Despite their high potential, only a limited number of *O*-alkyl hydroxylamines are commercially available. This work describes a new supported reagent which was used to synthesize in parallel a large diversity of *O*-alkyl hydroxylamines.

Result and Discussion

No parallel synthesis of *O*-alkyl hydroxylamines existed at the beginning of this project. Since then, a solution-phase synthesis based upon a capture-ring-

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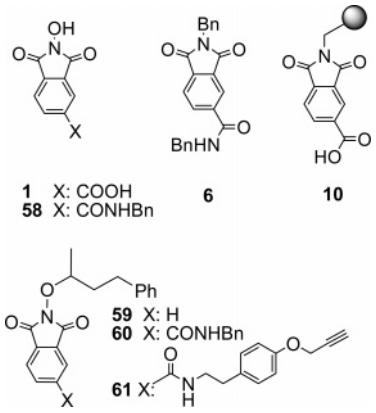
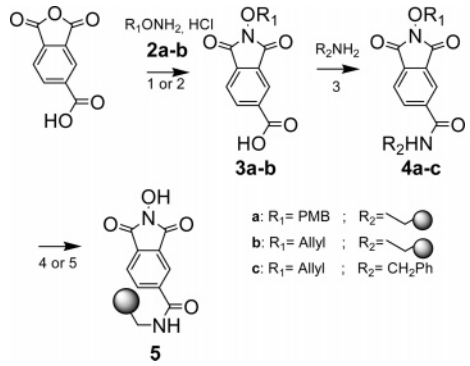
CHART 1



opening-metathesis polymerization release strategy[21] and a solid-phase synthesis using a polymer-supported *N*-hydroxyphthalimide[22] have been described. Both utilize a Mitsunobu alkylation of an *N*-hydroxyimide moiety as a key step. However, applications have been restricted either to a single step transformation or to activated alcohols as substrates which limits the diversity of the products. *O*-Alkyl hydroxylamines are classically obtained either by electrophilic amination of an alcohol[23−25] or by alkylation of an N-protected hydroxylamine derivative followed by its deprotection.[26−30] We therefore considered adapting one of these solution-phase methods to the solid phase in order to facilitate multiple step synthesis and to have access to high diversity. The strategy consisting of the alkylation of a supported *N*-hydroxyphthalimide followed by release of the free aminoxy compound in solution by hydrazinolysis or methylaminolysis[31] was selected. Indeed, a large variety of alkylating agents has been described and the volatility of the cleavage reagents allows their easy elimination. Our first generation of supported *N*-hydroxyphthalimides revealed itself to be identical with the one recently described by Porco et al.[22] but was obtained in a different manner. Its preparation was inspired by the report of Aronov et al.[32] concerning the synthesis of polymer-bound phthalimide. However, we observed that the selective *N*-hydroxyl protection of the *N*-hydroxy trimellitic imide **1** (Chart 1) with trityl chloride before coupling to an aminomethyl resin was a low-yielding process. As an alternative method, the condensation of trimellitic anhydride with *O*-trityl hydroxylamine in pyridine, also failed. However, the reaction of the easily accessible *O*-4-methoxybenzyl hydroxylamine hydrochloride[33] **2a** and of the commercially available *O*-allyl hydroxylamine hydrochloride **2b** under the same conditions succeeded, giving **3a** and **3b**, respectively, in good yields (Scheme 1).

SCHEME 1. Synthesis of the *N*-Hydroxyphthalimide-Supported Reagent 5[a]



[a] Reaction conditions: (1) Pyr, 90 °C, 24 h (**3a**: 95%; **3b**: 97%); (2) microwave (150 W), neat, 220 °C, 3 min (**3b**: 88%); (3) PyBOP, DIPEA, CH_2Cl_2; (4) **4b**, $Pd(PPh_3)_4$ $PhSiH_3$, CH_2Cl_2; (5) **4a**, TFA/CH_2Cl_2.

The *O*-allyl-protected derivative **3b** could also be obtained efficiently by a 3 min microwave irradiation (150 W) of the neat reactants. Coupling of the carboxylic acid **3b** with benzylamine, as a model of the aminomethyl resin amine, to give **4c** was first evaluated in solution under different conditions (coupling reagents, stoechiometry, base, solvents (data not shown)). The best result was obtained using acid **3b** in 2-fold excess and PyBOP as a coupling agent in the presence of DIPEA. Using benzylamine in excess resulted in formation of **6** (Chart 1) as the major compound through *O*-allyl *N*-hydroxyphthalimide aminolysis.

Attachment of the protected 4-methoxybenzyl **3a** and allyl **3b** derivatives to commercially available aminomethyl polystyrene (0.92 mmol/g, Acros) was performed under these optimized conditions to give the resins **4a** and **4b**, respectively. The reactions were monitored both by the primary amine Kaiser test[34] and by FT-IR analysis, following the carbonyl absorption (1737−1788 cm^{-1}). The loading of the *p*-methoxybenzyl (PMB) resin **4a** was estimated to be 0.69 mmol/g[35] (97% of the theoretical loading). Its deprotection was easily accomplished by acidic cleavage with TFA/CH_2Cl_2 (1/1) to afford resin **5** loaded at 0.78 mmol/g[36] (100% of the theoretical loading). Several conditions[37−40] were tested

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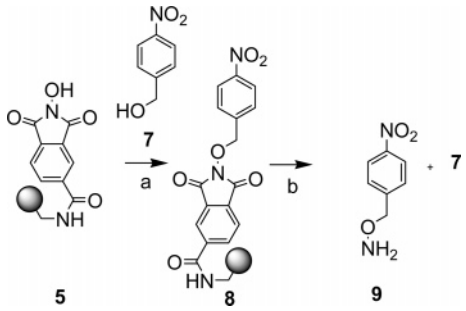
SCHEME 2. Synthesis of *O*-Alkyl Hydroxylamine 9 from 5[a]

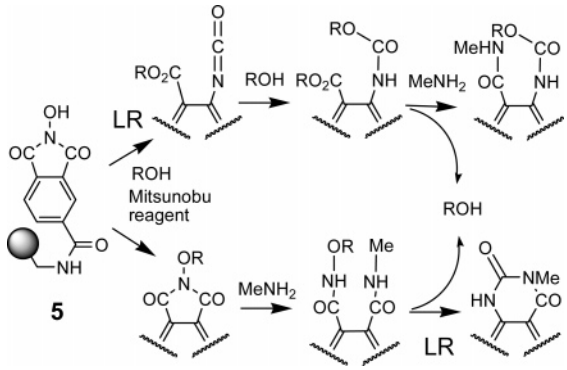


[a] Reaction conditions: (a) Mitsunobu reagents; (b) $MeNH_2$, $CHCl_3$/MeOH.

for cleavage of the allyl group of resin **4b** by following the disappearance of the allyl signal (δ: 4.56 ppm (2H); 5.28 ppm (2H); 5.95 ppm (1H)) in the HR-MAS analysis of the resin. The best results were obtained with tetrakis-(triphenylphosphine)palladium/phenylsilane[41] in CH_2Cl_2 at room temperature. The loading of this resin **5** was also 0.78 mmol/g[36] (100% of the theoretical loading). Among all possible methods for *N*-hydroxyphthalimide alkylation, we focused on the Mitsunobu reaction because of its scope, its stereospecificity, the mild reaction conditions,[42,43] and the large number of alcohols commercially available. We initially searched for optimum conditions using 4-nitrobenzyl alcohol, **7**, as the substrate (Scheme 2).

Despite trials with several reagents (Ph_3P, Bu_3P, DIAD, TMAD, sulfamide betaine[44]) under different conditions (solvent, temperature, order of reagent addition, reaction time, number of cycles) and regardless of the resin **5** used (from **4a** or **4b**), no reproducible results could be obtained, and simultaneous formation of the 4-nitrobenzyl alcohol **7** as secondary product was systematically observed after methylaminolysis.[45] The best result was obtained with the couple Bu_3P/TMAD[46] as already observed by Porco et al.,[22] but in 1,2-DCE as the solvent rather than in THF/CH_2Cl_2. The O-substituted hydroxylamine **9** was finally reproducibly obtained in 75% yield (based on **5**) but contamination by 10% of the alcohol **7** could not be avoided. This could not be due to nonspecific adsorption of the alcohol on the polymer since extensive washing with different solvents before cleavage did not modify the results. Although we cannot exclude the involvement of a Lossen rearrangement (LR in Scheme 3) at the aminolysis step[47] or during the Mitsunobu reaction,[48] leading to a supported anthranilate ester derivative and release of alcohol after methylaminolysis (Scheme 3), we rather suspect potential cross-linking and/

SCHEME 3. Involvement of Lossen Rearrangement (LR) as a Possible Mechanism for the Formation of Starting Alcohol



or formation of the N-supported phthalimide 6-carboxylic acid **10** (Chart 1) resulting from the reaction of the resin aminomethyl site with the *N*-alkoxyphthalimide moiety before or after coupling of the acid.[49]

The use of other commercially available aminomethyl resins differing in their polymer part[50] or of *N*-methylated aminomethyl polystyrene resin[51] did not solve the problem. Furthermore, we found that even under the best reaction conditions, only primary active alcohols such as benzyl, allyl, or propargyl gave consistent results.

Because of these disappointing results, we chose to introduce a spacer which would move the reactive site away from the polymer. As an additional constraint it should be attached to the resin by a reaction requiring a non-nucleophilic species. Recently, Löber et al.[52] demonstrated the possibility of replacing the amide by a 1,2,3-triazolyl linkage to the resin, obtained through Huisgen 1,3-dipolar cycloaddition of an azidomethyl resin and an alkyne. Using a similar strategy, we chose to intercalate an aminoethylphenoxymethyl group as a pseudo-rigid spacer between the reactive *N*-hydroxyphthalimide moiety and the polymer. We preferred to adopt a "preloading" strategy for the synthesis of this original nonintegral type of linker.[53] The precursor **13** of the linker was obtained from the inexpensive tyramine hydrochloride **11** through the known *N*-Boc derivative,[54] which after *O*-alkylation with propargyl bromide and Boc cleavage to give **12** was coupled with an excess of phthalimide derivative **3a** using PyBOP as coupling reagent (Scheme 4). During this last step, the amino compound generated from TFA salt **12** and DIPEA was added dropwise to the activated ester in order to avoid the *N*-alkylphthalimide side products. Cu(I)-promoted loading of purified **13** onto azido methyl polystyrene prepared from Merrifield resin (1.4 mmol/g) according to the Löber procedure[52] gave the O-protected supported reagent **15** with an estimated loading of 0.78 mmol/g (89% of the theoretical yield).[35] Cleavage of the

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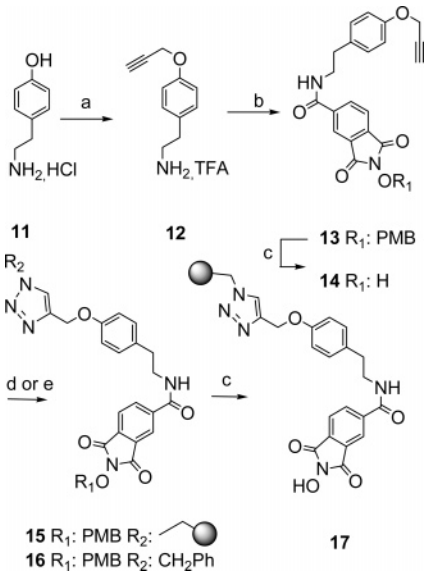
SCHEME 4. Synthesis of the Supported Reagent 17[a]



[a] Reaction conditions: (a) (1) Boc_2O, TEA, dioxane/H_2O, (2) propargyl bromide, K_2CO_3, DMF, (3) TFA/CH_2Cl_2, rt; (b) **3a**, PyBOP, DIPEA, CH_2Cl_2; (c) TFA/CH_2Cl_2, rt; (d) for **15**, azidomethyl polystyrene, CuI, DIPEA, THF, rt; (e) for **16**, $PhCH_2N_3$, CuI, DIPEA, THF.

TABLE 1. Influence of the Reagent for the Mitsunobu Reaction of the Resin 17

reagent/solvent	yield[a,b] (%)	purity[a,c] (%)
DIAD, Ph_3P/CH_2Cl_2[d]	56	>99
TMAD, Bu_3P/1,2-DCE[d]	34	80[e]
sulfamide betaine/CH_2Cl_2[f]	72	>99

[a] The yield and the purity were determined for the alkylation and methylaminolysis steps. [b] Determined by NMR analysis using cyclohexane as internal standard. [c] Determined by HPLC. [d] The alkylation reaction was carried out at rt for 24 h using 5 equiv of Mitsunobu reagent and of alcohol. The subsequent methylaminolysis was realized using the standard protocol. [e] Impurities were not identified and were different from 4-nitrobenzyl alcohol. [f] 6 equiv of the Mitsunobu reagent and 5 equiv of the alcohol were used.

PMB group with TFA treatment gave the *N*-hydroxyphthalimide resin **17** loaded at 0.80 mmol/g (93% of the theoretical yield).[55] The regioselectivity of the 1,3 dipolar cycloaddition on the solid phase could not be ascertained since carbon and proton resonances of the triazolyl portion were not observable by HR-MAS analysis regardless of the resin (**15**, **17**) and the tested conditions. However, since the model solution-phase reaction of **13** with benzyl azide under the same conditions led to only one regioisomer **16,** it is assumed that only one regioisomer was also formed in the solid-phase reaction. This result is in contrast with the nonregioselective transformation observed by Porco et al.[22] in the absence of the aminoethylphenoxy spacer.

The Mitsunobu reaction of **17** with primary benzyl alcohol **7** was then studied under three different conditions (Table 1). We were pleased to see that high purity and reproducibility were reached with this new resin whatever the conditions used, the sulfamide betaine giving the best result.[56]

(55) Determined by elemental analysis.

The generality of these conditions was evaluated on a range of structurally diverse alcohols (Chart 2, Table 2). All products were obtained in high purity. The yields with primary alcohols were moderate to good, being generally higher for the activated ones. In the case of secondary alcohols (entries 9 and 10, Table 2) the results were disappointing. Although Mitsunobu reaction is known for its sensitivity to steric effects,[57−62] several examples of *N*-hydroxyphthalimide alkylation with secondary alcohols in solution phase have been reported.[7,63−76] Furthermore, in the case of 1-phenylethane-1,2-diol, the secondary benzylic alcohol has been found to be even more reactive than the primary alcohol.[77] We considered several hypotheses to explain the different behavior of the supported reaction. The lack of reactivity of the *N*-hydroxyphthalimide moiety due to substitution on the phenyl ring in **17** was discarded by comparing the homogeneous reactions of 4-phenylbutan-2-ol with *N*-hydroxyphthalimide (NHPt) and with the two different *N*-hydroxyphthalimide derivatives **58, 14** to give the *N*-alkoxyphthalimide derivatives **59**, **60**, and **61** respectively (Table 3)

The nonsignificant difference in yields obtained with the three N-hydroxyphthalimide derivatives using DIAD/Ph_3P does not explain the absence of reactivity on the supported reagent. It is worth mentioning that, in contrast to the solid-phase study on the primary 4-nitrobenzyl alcohol **7** described above (Table 1), the best results for the solution-phase reaction of this secondary alcohol were obtained using DIAD/Ph_3P. This led us to reinvestigate the solid-phase Mitsunobu reaction of 4-phenylbutan-2-ol using this reagent. In addition, we simultaneously evaluated different solvents which are

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CHART 2. *O*-Alkyl Hydroxylamines Synthesized

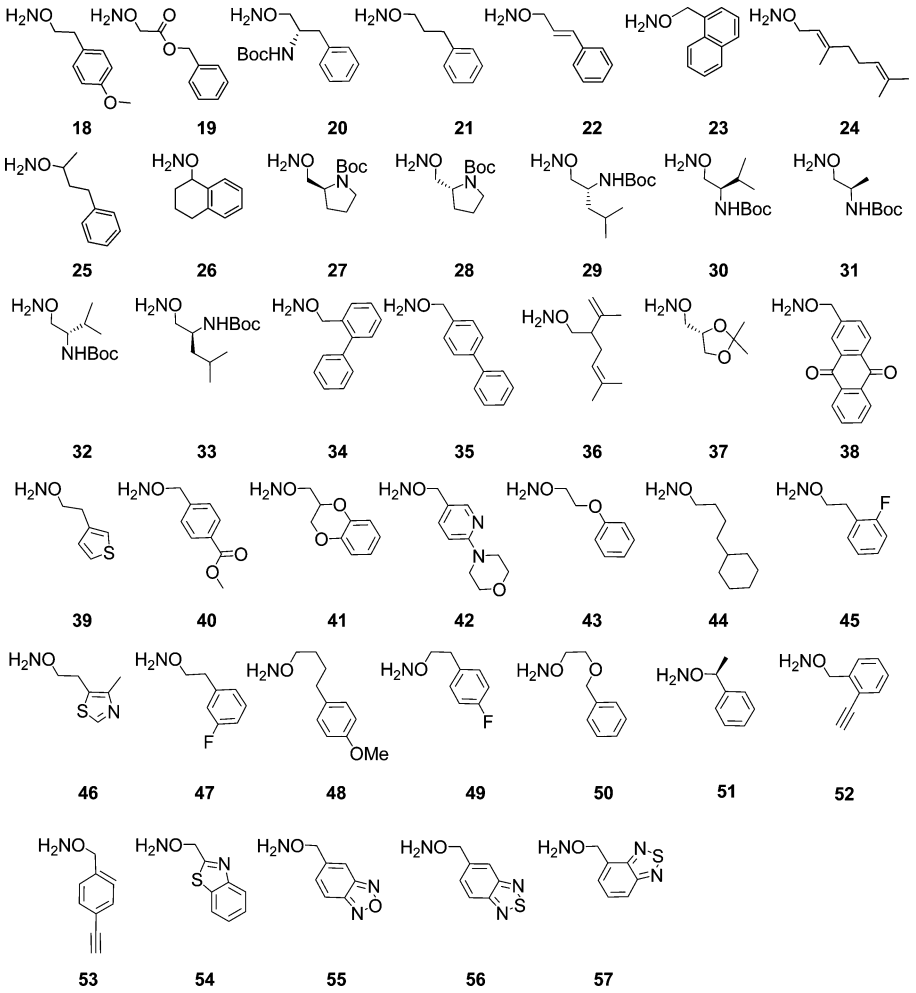


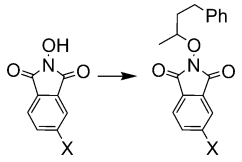
TABLE 2. Synthesis of *O*-Alkyl Hydroxylamines Using Sulfamide Betaine and Resin 17[a]

entry	$RONH_2$	yield,[b] % (purity, %)
1	**9**	70 (>99)[c]
2	**18**	92 (>99)[c]
3	**19**	44 (>95)[d]
4	**20**	70 (>95)[d]
5	**21**	54 (>95)[d]
6	**22**	72 (>95)[d]
7	**23**	74 (>95)[d]
8	**24**	59 (>95)[d]
9	**25**	20 (>95)[d]
10	**26**	0 (ND)

[a] The Mitsunobu reaction was carried out at rt during 24 h in CH_2Cl_2 using 6 equiv of sulfamide betaine and 5 equiv of alcohol. The subsequent methylaminolysis was realized using the standard protocol. [b] The yield was determined by NMR analysis of the *O*-alkyl hydroxylamines using cyclohexane as internal standard. [c] Purity determined by HPLC. [d] Purity determined by ^1H NMR.

known to influence the solid-phase synthesis and/or Mitsunobu reaction.[67,78–84] The results confirmed the superiority of the DIAD/Ph_3P reagent for the secondary alcohol and highlighted a solvent effect, especially with pyridine (Table 4).

TABLE 3. Solution-Phase Mitsunobu Reaction of *N*-Hydroxyphthalimide Model Derivatives[a] with 4-Phenylbutan-2-ol



	sulfamide betaine[a] yield[b] (%)	Ph_3P/DIAD[c] yield[b] (%)
NHPt[d]	52	73
58	35	65
14	27	62

[a] CH_2Cl_2 was used as solvent; see the Experimental Section for details. [b] Isolated products. [c] THF was used as solvent. [d] *N*-Hydroxyphthalimide.

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TABLE 4. Influence of Solvent and Reagent on the Mitsunobu Reaction of 4-Phenylbutan-2-ol with Resin 17

solvent	DIAD/Ph_3P[a] yield[b] (%)	Sulfamide betaine[c] yield[b] (%)
THF	24	<5
DMF	17	<5
EtOAc	0	0
CH_2Cl_2	42	20
pyridine	52	0

[a] The alkylation reaction was carried out at rt during 24 h using 5 equiv of Mitsunobu reagent and of alcohol. The subsequent methylaminolysis was realized using the standard protocol. [b] The yield was determined for the alkylation and methylaminolysis steps by NMR analysis of the *O*-alkyl hydroxylamine using cyclohexane as internal standard. [c] 6 equiv of the Mitsunobu reagent and 5 equiv of the alcohol were used.

TABLE 5. Influence of Base on the Mitsunobu Reaction with Resin 17 (Yield, % (Purity, %))[a,b]

		primary alkoxyamine		secondary alkoxyamine	
	base	**9**	**18**	**25**	**26**
1	none	56 (94)	60 (93)	24 (90)	0 (ND)
2	TMB[c]	61 (>95)	59 (>95)	22 (97)	22 (91)
3	TEA[d]	84 (96)	100 (92)	81 (93)	32 (81)
4	DMAP	84 (94)	98 (93)	68 (92)	38 (85)
5	$^iPr_2NH$	86 (94)	100 (>95)	93 (>95)	49 (87)
6	Im[e]	100 (93)	100 (92)	100 (93)	50 (93)
7	NMM[f]	88 (95)	100 (94)	92 (91)	28 (80)
8	DABCO	76 (89)	36 (94)	21 (94)	<5 (ND)

[a] The yield and the purity were determined for the alkylation and methylaminolysis steps by NMR analysis of the *O*-alkyl hydroxylamine using cyclohexane as internal standard. [b] The alkylation reactions were carried out at rt during 24 h using 5 equiv of Ph_3P/DIAD/base/alcohol in CH_2Cl_2. The subsequent methylaminolysis was realized using the standard procedure. [c] 1,1,3,3-Tetramethyl butylamine. [d] Triethylamine. [e] Imidazole.[f] *N*-Methylmorpholine.

Previous reports relating the beneficial action of a base on the Mitsunobu reaction[85−92] together with the mechanism recently proposed to account for this effect[93] suggest that the yield improvement with pyridine results from its basic character. This was confirmed by testing a series of bases on the alkylation of resin **17** with four different representative alcohols (Table 5).

All the tested amines except DABCO improved the yield of the Mitsunobu alkylation, especially with the secondary alcohols, without affecting the product purity. No correlation between the pK_a of the amine and the activation could be detected. This effect was particularly remarkable with imidazole (entry 6, Table 5), which was therefore selected as the base of choice for generalization

TABLE 6. Parallel Synthesis of *O*-Alkyl Hydroxylamine Using Resin 17 under Optimized Mitsunobu Reaction Conditions[a]

$RONH_2$[b]	yield,[c] %(purity, %)[d]	$RONH_2$[b]	yield,[c] % (purity, %)[d]
19	90 (93)	**20**	90 (>99)
21	88 (99)	**22**	61 (93)
23	51 (>99)	**24**	54 (>99)
27	94 (97)	**28**	92 (97)
29	83 (98)	**30**	82 (97)
31	72 (>99)	**32**	86 (96)
33	81 (96)	**34**	69 (94)
35	57 (95)	**36**	78 (93)
37	90 (98)	**38**	57[e] (>95)[f]
39	90 (98)	**40**	76 (>99)
41	83 (98)	**42**	45[e] (96)
43	84 (>99)	**44**	75 (>99)
45	59 (>99)	**46**	67 (>99)
47	62 (>99)	**48**	70 (>99)
49	60 (>99)	**50**	78 (>99)
51	62 (94)[g]	**52**	45 (91)[f]
53	52 (93)[f]		

[a] The Mitsunobu reaction was carried out at rt during 24 h in CH_2Cl_2 using 5 equiv of Ph_3P/DIAD/imidazole. The subsequent methylaminolysis was realized using the standard protocol. [b] Refer to Chart 2 for the structure of *O*-alkyl hydroxylamines. [c] The yield was determined by NMR analysis of the *O*-alkyl hydroxylamines using cyclohexane as internal standard. [d] Determined by GPC (see the Experimental Section). [e] The yields are underestimated because of the low solubility of the product in the NMR solvent. [f] Determined by NMR. [g] Yield and chemical and optical purities were determined by chiral HPLC (see the Experimental Section).

TABLE 7. Comparison of the Efficiency of Resin 17 and 5

$RONH_2$	resin **17**[a] (%)	resin **5**[a] (%)	resin **5**[b] (%)
18	100	42	18
25	100	24	0
26	50	22	0

[a] The Mitsunobu reaction was carried out at rt during 24 h in CH_2Cl_2 using 5 equiv of Ph_3P/DIAD/imidazole. The subsequent methylaminolysis was realized using the standard protocol. [b] Using Porco's conditions.[22]

of our approach. As shown in Table 6, the method was general and efficient, giving the *O*-alkyl hydroxylamine in high purity without purification. We also tested these new conditions with the first supported reagent **5** and found a beneficial effect of imidazole (see Table 7) but much less significant than with **17** and not sufficient to justify its utilization, thus demonstrating a specific linker effect. Furthermore, the base effect turned out to be catalytic since, although slightly less efficient, it was still noticeable with 0.1 equiv of imidazole (**18** and **25** were obtained in 79% and 60% yield, respectively). In addition, we verified the stereoselectivity of the Mitsunobu reaction with complete inversion of configuration on the (*R*)-1-phenylethanol, giving the corresponding (*S*)-*O*-alkyl hydroxylamine **51**.[94−95] This result confirmed the interest of the method for the asymmetric synthesis of optically active compounds. Furthermore, to compare this approach with the one previously described by Porco et al.,[22] three different alkoxyamines were synthesized using resin **17** or resin **5**. The results shown in Table 7 definitely established the superiority of the first linker

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TABLE 8. Synthesis of *O*-Alkyl Hydroxylamines from Benzyl Bromides with Resin 17

$RONH_2$	yield[a] (%)	purity[b] (%)
54	100	99
55	100	96
56	100	96
57	100	98

[a] The yield was determined for the alkylation and methylaminolysis steps by NMR analysis of the *O*-alkyl hydroxylamine using cyclohexane as internal standard. [b] Determined using GC−MS.

and of the imidazole-catalyzed Mitsunobu conditions. (Table 7).

Interestingly, the diversity of the *O*-alkyl hydroxylamines synthesized could be increased by alkylation of the *N*-hydroxyphthalimide-supported reagent **17** with alkyl bromide using triethylamine in DMF at room temperature to afford after methylaminolysis the corresponding *O*-alkyl hydroxylamine with high purity and efficiency (Table 8).

Conclusion

In this study, we have devised a new polymeric *N*-hydroxypthalimide reagent carrying a novel linker useful for the parallel synthesis of highly diverse *O*-alkyl hydroxylamines. The replacement of an amide by a triazolyl heterocycle to connect the linker to the resin and the introduction of a tyramine-like spacer allowed a more efficient and cleaner synthesis. In addition, this study points out a specific base effect in the Mitsunobu reaction. Further studies to understand the mechanism of this effect and to enhance the diversity of the *O*-alkyl hydroxylamines which can be prepared by this multistep solid-phase synthesis will be described in due course.

Experimental Section

O-*p*-Methoxybenzylhydroxylamine hydrochloride and *N*-(*tert*-butoxycarbonyl) by tyramine were obtained as previously described.[33,54] Betaine sulfamide was obtained according to the procedure of Castro et al.[44]

2-(4-Methoxybenzyloxy)-1,3-dioxoisoindoline-5-carboxylic Acid (3a). To a magnetically stirred solution of *O*-*p*-methoxybenzyl hydroxylamine hydrochloride (5.80 g, 30.5 mmol) in pyridine (45 mL) at 90 °C was added trimellitic anhydride (5.33 g, 27 mmol). The reaction mixture was stirred for 24 h at 90 °C and then concentrated in vacuo. The solid residue was partitioned between EtOAc and 1 N aqueous HCl. The organic phase was washed with brine and water and dried ($MgSO_4$). Evaporation under reduced pressure provided the desired product as a white solid (8.40 g, 95%): mp 199−200 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) 3.75 (s,3 H), 5.11 (s, 2 H), 6.97 (d, J = 8.7 Hz, 2 H), 7.45 (d, J = 8.7 Hz, 2 H), 7.99 (d, J = 7.7 Hz, 1 H), 8.20 (s, 1 H), 8.37 (d, J = 7.7 Hz,1 H), 13.7 (1H, sl); ^{13}C NMR (DMSO-d_6) δ 54.8, 78.7, 113.5, 122.8, 123.4, 125.8, 128.8, 131.2, 131.7, 135.2, 136.1, 159.6, 162.1 (2), 165.4; FT-IR (KBr) ν_{max} 3100, 1784, 1715, 1610, 1513, 990 cm^{-1}; ESI-MS (+) 350 (M + Na), 382 (M + Na + MeOH); HRMS calcd for $C_{17}H_{13}NO_6Na$ 350.0680, found 350.0641. Anal. Calcd for $C_{17}H_{13}NO_6$: C, 62.39; N, 4.00; O, 29.33. Found: C, 62.19; N, 4.18; O, 29.31.

2-(Allyloxy)-1,3-dioxoisoindoline-5-carboxylic Acid (3b). Procedure A. Solid trimellitic anhydride (6.0 g, 31.2 mmol) was heated at 200 °C by microwave irradiation (150 W), and *O*-allyl hydroxylamine hydrochloride (3.7 g, 33.7 mmol) was added to the mixture. The reaction mixture was stirred for 3 min then cooled to room temperature. The solid was partitioned between water (30 mL) and CH_2Cl_2 (100 mL). The organic layer was dried ($MgSO_4$) and evaporated to provide **3b** as a white solid (6.78 g, 88%), identical to the product obtained from the following procedure.

Procedure B. To a magnetically stirred solution of *O*-allyl hydroxylamine hydrochloride (627 mg, 6.13 mmol) in pyridine (4.50 mL) at 90 °C was added trimellitic anhydride (1.00 g, 5.20 mmol). The reaction mixture was stirred for 24 h at 90 °C and then concentrated in vacuo. The solid residue was diluted with EtOAc and washed with 1 N aqueous HCl, brine, and water. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to provide the desired product as a white solid (1.21 g, 94%): mp 195 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.64 (d, J = 6.5 Hz, 2 H), 5.33 (dd, J = 10.3, 1.4 Hz, 1 H), 5.41 (dd, J = 17.2, 1.4 Hz, 1 H), 6.05 (m,1 H), 7.99 (d, J = 7.7 Hz, 1 H), 8.19 (s, 1 H), 8.36 (d, J = 7.7 Hz, 1 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 78.2, 121.9, 123.1, 123.6, 128.9, 131.6, 131.8, 135.5, 136.4, 162.4 (2C), 165.6; FT-IR (ATR) ν_{max} 2944, 1884, 1730, 1681, 1643, 987 cm^{-1}; ESI MS (+) 302.7 (M + Na + MeOH); HRMS calcd for $C_{13}H_{13}NO_6Na$ 302.064, found 302.068. Anal. Calcd for $C_{12}H_9NO_5$: C, 58.30; N, 5.67; O, 32.36. Found: C, 58.07; N, 5.55; O, 32.37.

2-(Allyloxy)-*N*-benzyl-1,3-dioxoisoindoline-5-carboxamide (4c). To a stirred solution of **3b** (100 mg, 0.40 mmol) in DMF/CH_2Cl_2 (1/2, 15 mL) was added DIC (63.4 μL, 0.40 mmol) at rt. The reaction mixture was stirred for 30 min at room temperature, and benzylamine (21.8 μL, 0.20 mmol) was added dropwise over 5 min and stirred for 3 h at the same temperature. The solution was evaporated in vacuo. The mixture was diluted with CH_2Cl_2 and washed with water. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2−MeOH, 98:2) to yield the desired product (98 mg, 72%) which was crystallized from EtOAc (70 mg, 51%): mp 134−136 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.68−4.73 (m, 4 H), 5.37 (m, 2H), 6.12 (m, 1 H), 6.53 (sl, 1 H), 7.37 (m, 5 H), 7.92 (d, J = 7.7 Hz, 1 H), 8.18 (d, J = 1.5 Hz, 1 H), 8.24 (dd, J = 1.5, J = 7.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 44.6, 79.0, 121.6, 122.9, 124.0, 128.0, 128.0, 128.7, 129.0, 131.0, 131.1, 132.0, 133.7, 137.3, 140.4, 162.8 (2C), 164.9; FT-IR (ATR) ν_{max} 3281, 2971, 1780, 1726, 1634, 1538, 990 cm^{-1}; ESI MS (+) 359.1 (M + Na); HRMS calcd for $C_{19}H_{16}N_2O_4Na$ 359.1008, found 359.0992.

***N*-Hydroxyphthalimide Resin (5). From the Allyl Derivative (3b).** To a solution of **3b** (1.82 g, 4 equiv) in CH_2Cl_2 (200 mL) were added PyBOP (4.48 g, 5 equiv) and DIPEA (3.2 mL, 10 equiv). The mixture was stirred for 1 h, and the dark-orange solution was added to a pre-swollen (CH_2Cl_2) aminomethylated polystyrene resin (Acros, 0.92 mmol/g, 2.0 g, 1.84 mmol). The suspension was stirred mechanically for 24 h at room temperature and monitored using the Kaiser test.[34] After filtration, the resin **4b** was washed with CH_2Cl_2 (3 × 50 mL), DMF (3 × 50 mL), MeOH (3 × 50 mL), CH_2Cl_2 (50 mL), MeOH (50 mL), and CH_2Cl_2 (50 mL) and dried under reduced pressure (2.38 g): MAS ^{1}H NMR ($CDCl_3$ + DMSO-d_6 drop, 400 MHz) δ 4.40, 4.57, 5.23, 5.98, 7.74, 8.28, 8.35, 9.0; MAS ^{13}C NMR ($CDCl_3$, 100 MHz) 79.0, 122.1, 122.9, 124.3, 129.4, 131.1, 134.0 (determined from HMBC et HMQC spectra analysis); FT-IR (ATR) ν_{max} 3021, 2920, 1789, 1732, 1668, 997 cm^{-1}. For the deprotection of the resin, $Pd(PPh_3)_4$ (224 mg, 0.1 equiv) and $PhSiH_3$ (1.06 mL, 5 equiv) in CH_2Cl_2 (240 mL) were added to the pre-swollen resin (CH_2Cl_2) and the suspension stirred for 24 h at room temperature. After filtration, the resin was washed with a mixture of acetic acid in DMF (2% (v/v)), CH_2Cl_2 (3 × 50 mL), DMF (3 × 50 mL), MeOH (3 × 50 mL), CH_2Cl_2 (50 mL), MeOH (50 mL), and CH_2Cl_2 (50 mL). Three cycles of deprotection and washing were done. The resin was then dried under reduce pressure (2.38 g, loading 0.78 mmol). The FT-IR (ATR) spectrum was found identical with that of the following resin obtained from **3a**.

From the PMB Derivative (3a). To a solution of **3a** (1.20 g, 4 equiv) in CH_2Cl_2 (100 mL) were added PyBOP (2.24 g, 5 equiv) and DIPEA (1.6 mL, 10 equiv). After being stirred for 1 h, the dark-orange solution was mixed with pre-swollen (CH_2Cl_2) aminomethylated polystyrene resin (Acros, 0.92 mmol/g, 1.0 g, 1 equiv). The suspension was stirred for 24 h at room temperature and monitored using the Kaiser test. After filtration, the resin **4a** was washed with CH_2Cl_2 (3 × 20 mL), DMF (3 × 20 mL), MeOH (3 × 20 mL), CH_2Cl_2 (20 mL), MeOH (20 mL), and CH_2Cl_2 (20 mL) and dried under reduced pressure (m = 1.35 g, loading: 0.69 mmol/g): MAS ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.67, 5.08, 6.79, 7.35, 7.75, 8.07; MAS ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.3, 79.7, 114.0, 121.8, 123.8, 125.6, 130.9, 131.7, 133.8, 160.5, 162.7, 165.0; FT-IR (ATR) ν_{max} 3023, 2920, 1787, 1733, 1669, 997 cm^{-1}. The resin was deprotected for 1 h in a mixture of TFA−CH_2Cl_2 (1:1, 20 mL) before filtration. This operation was repeated twice. The resin was washed with CH_2Cl_2 (3 × 20 mL), DMF (3 × 20 mL), MeOH (3 × 20 mL), CH_2Cl_2 (20 mL), MeOH (20 mL), and CH_2Cl_2 (20 mL) and dried under reduced pressure. (1.20 g, loading: 0.78 mmol/g): MAS ^{1}H NMR ($CDCl_3$ + DMSO-d_6 1drop, 400 MHz) δ 4.49, 7.80, 8.29, 8.35; MAS ^{13}C NMR ($CDCl_3$ + DMSO-d_6 1drop, 100 MHz) δ 42.9, 121.4, 125.2, 128.2, 130.1, 133.2, 139.6, 139.6, 163.2, 164.5; FT-IR (ATR) ν_{max} 3023, 2920, 1787, 1725, 1648, 995 cm^{-1}.

***O*-Propargyltyramine, Trifluoroacetate Salt (12).** To a stirred solution of *N*-Boc-tyramine (11.6 g, 48.9 mmol) in DMF (100 mL) were added K_2CO_3 (8.5 g, 58.7 mmol) and propargyl bromide (80% solution in toluene, 6.93 mL, 58.7 mmol). The solution was stirred overnight at 70 °C. After evaporation under reduced pressure, the residue was dissolved in EtOAc and the solution washed with a 10% aqueous citric acid and brine. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, EtOAc−Hept 5:95) to give the *N*-Boc-*O*-propargyl tyramine (12.1 g). A solution of this product in TFA−CH_2Cl_2 (4:6; 200 mL) was stirred for 3 h at room temperature. After concentration under reduced pressure, the residue was redissolved in acetonitrile and the solvent evaporated in vacuo. This operation was repeated twice to provide **12** as a white solid which was washed with Et_2O (3 × 50 mL) (10.2 g, 80%): mp 114 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2,79 (t, J = 6.9 Hz, 2H), 3.01 (t, J = 6.9 Hz, 2H), 3.56 (t, J = 2.4 Hz, 1H), 4.77 (d, J = 2.4 Hz, 2 H), 6.95 (d, J = 8.7 Hz, 2H), 7.19 (d, J = 8.7 Hz, 2H), 7.84 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 32.1, 55.2, 78.1, 79.25, 80.7, 114.9, 129.6, 129.8, 156.0; FT-IR (ATR) ν_{max} 3301, 1734, 1660, 1512, 1203, 1130 cm^{-1}; ESI MS (+) 176,10 (M + H), 159,06 (M − NH_3). Anal. Calcd for $C_{12}H_9NO_5$: C, 53.98; H, 4.88; N, 4.84; O, 16.59. Found: C, 53.85; H, 4.95; N, 5.05.

2-(4-Methoxybenzyloxy)-1,3-dioxo-*N*-(4-(prop-2-ynyloxy)phenethyl)isoindoline-5-carboxamide (13). To a magnetically stirred suspension of **3a** (8.40 g, 25.6 mmol) in CH_2Cl_2 (380 mL) were added PyBOP (13.34 g, 25.6 mmol) and DIPEA (8.94 mL, 51.3 mmol) in one portion. The solution became homogeneous within minutes and became dark after 1 h at room temperature. A suspension of *O*-propargyltyramine trifluoroacetate salt (3.70 g, 12.8 mmol) and DIPEA (2.23 mL, 12.8 mmol, 0.5 equiv) in CH_2Cl_2 (40 mL) was added dropwise. The reaction mixture was stirred for 24 h at room temperature and monitored by thin-layer chromatography (silica gel, CH_2Cl_2−AcOEt, 8:2, R_f 0.4). The mixture was washed with 1 N aqueous HCl and with water. The organic layer was dried ($MgSO_4$) and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2−EtOAc 95:5). After evaporation under reduced pressure, the product was washed with Et_2O to yield a white solid (5.77 g, 93%): mp 199−200 °C; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 2.53 (t, J = 2.4 Hz, 1H), 2.90 (t, J = 6.8 Hz, 2H), 3.71 (dd, J = 5.9, J = 6.8 Hz, 2 H), 3.79 (s, 3 H), 4,68 (d, J = 2.4 Hz, 2 H), 5.15 (s, 2 H), 6.17 (t, J = 5.9 Hz, 1H), 6.87 (d, J = 8.7 Hz, 2 H), 6.94 (d, J = 8.7 Hz, 2H), 7.16 (d, J = 8.7 Hz, 2H), 7.42 (d, J = 8.7 Hz, 2 H), 7.85 (d, J = 7.9 Hz, 1 H), 8.01 (d, J = 1.4 Hz, 1 H), 8.10 (dd, J = 1.4, J = 7.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.7, 41.7, 55.4, 56.0, 75.7, 76.9, 79.7, 114.1, 115.4, 121.6, 124.0, 125.7, 129.8, 131.0, 131.4, 131.8, 132.0, 133.6, 140.5, 156.4, 160.1, 162.1, 163.2, 165.1; FT-IR (ATR) ν_{max} 3286, 2961, 1786, 1723, 1638, 1610, 1025 cm^{-1}; ESI-MS (+) 539.1 (M + Na + MeOH); HRMS calcd for $C_{29}H_{28}N_2O_7Na$ 539.1794, found 539.1778. Anal. Calcd for $C_{28}H_{24}N_2O_6 \cdot {}^1/_2H_2O$: C, 68.14; H, 5.11; N, 5.68; O, 21.07. Found: C, 68.53; H, 4.84; N, 5.63; O, 20.64.

2-Hydroxy-1,3-dioxo-*N*-(4-(prop-2-ynyloxy)phenethyl)-isoindoline-5-carboxamide (14). Compound **13** was added at room temperature to a mixture of CH_2Cl_2−TFA (5:5, 50 mL). The mixture which became red after 1 h was stirred for a further 2 h then concentrated in vacuo. The residue was diluted with acetonitrile and evaporated under reduced pressure. This procedure was repeated three times. The crude product was suspended in CH_2Cl_2 (10 mL) and filtered to yield a yellow solid (755 mg, 100%): mp 183 °C; ^{1}H NMR (DMSO-d_6) δ 2.81 (t, J = 7.2 Hz, 2 H), 3.44−3.56 (m,3 H), 4.77 (d, J = 2.1 Hz, 2 H), 6.92 (d, J = 8.4 Hz, 2 H), 7.20 (d, J = 8.4 Hz, 2 H), 7.93 (d, J = 7.4 Hz, 1H), 8.25 (s, 1 H), 8.26 (d, J = 7.4 Hz, 1 H), 8.94 (t, J = 5.4 Hz, 1 H) 10.93 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 33.9, 41.2, 55.2, 78.0, 79.3, 114.6, 121.1, 123.0, 129.0, 129.5, 130.7, 131.9, 133.4, 141.0, 155.6, 163.5, 163.6, 165.0.; FT-IR (ATR) ν_{max} 3372, 3262, 1788, 1720, 1626 cm^{-1}; ESI-MS (+) 365.1 (M + 1); 387.1 (M + Na + MeOH); HRMS calcd for $C_{20}H_{16}N_2O_5Na$ 387.0957, found 587.0927.

Triazole-Linked *N*-*p*-Methoxybenzyloxyphthalimide Resin (15). To a preswollen Merrifield resin (Acros, dvb 2%, 1.4 mmol/g, 2.8 g, 3.9 mmol) in DMSO (26 mL) was added NaN_3 (1.26 g, 19.4 mmol, 5 equiv). The mixture was stirred mechanically at 60 °C for 48 h, and the resin was filtered, washed with DMSO (3 × 50 mL), CH_2Cl_2 (3 × 50 mL), DMF (3 × 50 mL), MeOH (3 × 50 mL), CH_2Cl_2 (50 mL), MeOH (50 mL), and CH_2Cl_2 (50 mL), and dried under reduced pressure (2.55 g) (FT-IR ν_{max} 3028, 2915, 2092, 1597, 1495, 1456, 1272, 1251, 754, 698 cm^{-1}). To the azidomethyl polystyrene resin pre-swollen in THF (47 mL) were added **13** (5.28 g, 3.0 equiv), CuI (69 mg, 0.1 equiv), and DIPEA (13 mL). The suspension was stirred mechanically at 35 °C. Reaction was stopped after total disappearance of the IR signal of the azido group (2096 cm^{-1}). The resin was filtered and washed with THF (3 × 50 mL), DMF−H_2O (1:1, 3 × 50 mL), pyridine (3 × 50 mL), DMF (50 mL), CH_2Cl_2 (3 × 50 mL), DMF (3 × 50 mL), MeOH (3 × 50 mL), CH_2Cl_2 (50 mL), MeOH (50 mL), and CH_2Cl_2 (50 mL). Drying of the residue in vacuo gave the resin (4.57 g) showing an IR signal for phthalimide at 1735−1788 cm^{-1}. The excess of **13** could be recycled by evaporation of the filtrate. The crude product was dissolved in CH_2Cl_2 and the organic layer washed with water, dried ($MgSO_4$) then concentrated in vacuo. The residue was washed with diethyl ether to give the crude derivative **13** (1.95 g, 4.0 mmol). The loading of the resin was determined to be 0.75 mmol/g (93% of the theoretical yield) by the gravimetric method: MAS ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.92, 3.73, 5.13, 6.84, 7.41, 7.76, 8.19; MAS ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.6, 41.8, 55.3, 79.7, 114.0, 114.8, 122.1, 123.7, 125.7, 129.0, 129.9, 130.7, 131.7, 133.8, 140.8, 156.9, 160.5, 162.9, 165.6; FT-IR (ATR) ν_{max} 2920, 1787, 1730, 1661, 1610, 1513, 979 cm^{-1}.

Triazole-Linked *N*-Hydroxyphthalimide Resin (17). Resin **15** (4.57 g, 0.78 mmol/g, 3.4 mmol) was suspended in a mixture of CH_2Cl_2−TFA (1:1, 45 mL) at room temperature and stirred for 1 h. The resin was filtered and treated again with the CH_2Cl_2−TFA mixture for 1 h. The resin was washed with CH_2Cl_2 (3 × 50 mL), DMF (3 × 50 mL), MeOH (3 × 50 mL), CH_2Cl_2 (50 mL), MeOH (50 mL), and CH_2Cl_2 (50 mL) and dried under reduced pressure (4.05 g). Loading was determined by elemental analysis: 0.8 mmol/g (93% of the theoretical yield) and by the Fmoc test: 0.9 mmol/g (104% of the theoretical yield); FT-IR (KBr) ν_{max} 1735−1788 cm^{-1} (νCO phthalimide); MAS ^{1}H NMR ($CDCl_3$ + DMSO-d_6 1 drop, 400 MHz) δ 2.8,

3.6, 6.9, 7.1, 7.8, 8.3, 8.75, 10.9; ^{13}C NMR ($CDCl_3$ + DMSO-d_6 1 drop, 100 MHz) δ 34.1, 41.6, 114.4, 121.5, 122.7, 128.9, 129.5, 130.7, 131.6, 133.4, 139.9, 156.9, 163.4, 163.5, 165.6; FT-IR (ATR) ν_{max} 3023, 2920, 1787, 1723, 1648, 1600, 1538, 1507, 1492, 1451, 1302, 1251, 1197, 1179, 1138, 1115, 985, 920, 815, 756, 698 cm^{-1}. Anal. Found: N, 5.19; O, 6.47.

***N*-(4-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenethyl)-2-(4-methoxybenzyloxy)-1,3-dioxoisoindoline-5-carboxamide (16).** To a magnetically stirred suspension of **13** (300 mg, 0.62 mmol) in THF (3 mL) were added benzyl azide (77 μL, 0.62 mmol), CuI (12.0 mg, 0.06 mmol, 0.1 equiv), and DIPEA (0.5 mL). The suspension was stirred at 35 °C for 24 h, filtered, and washed with CH_2Cl_2 (5 mL), MeOH (5 mL), water (5 mL), MeOH (5 mL), and CH_2Cl_2 (5 mL) to give **16** (335 mg, 90% pure (see HPLC), 78%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.80 (t, J = 7.3 Hz, 2H), 3.48 (td, J = 8.1 Hz, J = 16.7 Hz, 2 H), 3.76 (s, 3 H), 5.09 (s, 2 H), 5.10 (s, 2 H), 5.60 (s, 2 H), 6.95 (d, J = 8.5 Hz, 2 H), 6.95 (d, J = 8.5 Hz, 2 H), 7.16 (d, J = 8.5 Hz, 2 H), 7.34 (m, 5 H), 7.43 (d, J = 8.5 Hz, 2 H), 7.94 (d, J = 7.7 Hz, 1 H), 8.23 (s, 1 H), 8.25 (dd, J = 1.5 Hz, J = 7.7 Hz, 1 H), 8.26 (d, J = 1.5 Hz, 1 H), 8.92 (t, J = 5.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.0, 162.6, 162.5, 159.8, 156.4, 143.4, 139.9, 135.9, 133.6, 131.5, 131.4, 130.4, 129.5, 128.7, 128.6, 128.0, 127.8, 125.5, 124.4, 123.3, 121.2, 114.5, 113.7, 78.8, 60.9, 55.0, 52.7, 41.1, 33.8; FT-IR (ATR) ν_{max} 2919, 1788, 1722, 1649 cm^{-1}; ESI-MS (+) 640.2 (M + Na); HRMS calcd for $C_{29}H_{28}N_2O_7Na$ 640.2172, found 640.2183. The chemical purity was determined to 90% by HPLC analysis using an analytical Atlantis-C_{18} column (150 × 4.6 mm, 5 μm). Detection was at 234 nm using a photodiode array detector: solvent A, water; solvent B, acetonitrile; 50% solvent B, 5 min, 50−80% solvent B in 5 min, 1.0 mL min^{-1}.

Solution-Phase Mitsunobu Reaction of *N*-Hydroxyphthalimide Model Derivatives. With Sulfamide Betaine. Betaine sulfamide (61 mg, 0.15 mmol) was added in one portion to a solution of the *N*-hydroxyphthalimide derivative (0.136 mmol) and 4-phenylbutan-2-ol (32 μL, 0.21 mmol) in CH_2Cl_2 (4.5 mL). After the mixture was stirred for 24 h at room temperature, a new portion of betaine sulfonamide (61 mg, 0.15 mmol) was added and the mixture was stirred for 1 more day. The solution was evaporated under reduced pressure and the crude product was purified by flash chromatography on silica gel (heptane−AcOEt mixture). The yields obtained with N-hydroxyphthalimide, **58** or **14** as substrate are given in Table 3.

With Ph_3P/DIAD. DIAD (30 μL, 0.15 mmol) was added dropwise to a solution of the *N*-hydroxyphthalimide derivative (0.136 mmol), triphenylphosphine (39 mg, 0.15 mmol), and 4-phenylbutan-2-ol (32 μL, 0.21 mmol) in dry THF (2.1 mL) at room temperature. The yellow solution was stirred for 24 h and concentrated under reduced pressure, and the crude product was purified by flash chromatography on silica gel (heptane-AcOEt mixture). The yields obtained with *N*-hydroxyphthalimide, **58**, or **14** as substrate are given in Table 3.

2-(4-Phenylbutan-2-yloxy)isoindoline-1,3-dione (59): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.35 (d, J = 6.2 Hz, 3 H), 1.92 (m,1 H), 2,10 (m, 1 H), 2.87 (t, J = 8.0 Hz, 2 H), 4.42 (m, 1 H), 7.10−7.30 (m, 5 H), 7.73 (dd, J = 3.1, J = 5.5 Hz, 2 H), 7.83 (dd, J = 3.1, J = 5.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 18.9, 31.4, 36.8, 83.8, 123.5, 125.9, 128.4, 128.5, 129.0, 134.4, 141.7, 164.4; FT-IR (ATR) ν_{max} 2931, 1788, 1727 cm^{-1}; ESI MS (+) 318.2 (M + Na); HRMS calcd for $C_{18}H_{17}NO_3Na$ 318.1106, found 318.1104.

***N*-Benzyl-1,3-dioxo-2-(4-phenylbutan-2-yloxy)isoindoline-5-carboxamide (60):** ^{1}H NMR ($CDCl_3$, 300 MHz) 1.35 (d, J = 6.0 Hz, 3 H), 1.84 (m, 1 H), 2.10 (m, 1 H), 2.80 (t, J = 8.0 Hz, 2 H), 4.35 (m, 1 H), 4.55 (d, J = 5.9 Hz, 2 H), 6.60 (m, 1 H), 7.25−7.35 (m, 10 H), 7.80 (d, J = 7.9 Hz, 1 H), 8.10 (s, 1 H), 8.20 (d, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 14.1, 31.4, 36.7, 44.5, 84.0, 121.1, 123.9, 125.9, 127.9, 128.0, 128.4, 128.5, 128.9, 129.30, 131.1, 133.8, 137.3, 140.3, 141.5, 163.5, 163.6, 165.0; FT-IR (ATR) ν_{max} 3316, 2925, 1785, 1731, 1644 cm^{-1}; ESI MS (+) 483.2 (M + Na + MeOH); HRMS calcd for $C_{27}H_{28}N_2O_5Na$ 483.1896, found 483.1917.

***N*-[4-(But-3-ynyl)phenethyl]-1,3-dioxo-2-(4-phenylbutan-2-yloxy)isoindoline-5-carboxamide (61):** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.37 (d, J = 6,2 Hz, 3 H), 1.92 (m, 1 H), 2.12 (m, 1 H), 2.54 (t, J = 2.3 Hz, 1 H), 2.90 (m, 4 H), 3.72 (m, 2 H), 4.43 (m, 1 H), 4.68 (d, J = 2.3 Hz, 2 H), 6.31 (m, 1 H), 6.94 (d, J = 8.6 Hz, 2 H), 7.16 (d, J = 8.6 Hz, 2 H), 7.27 (m, 5 H), 7.89 (d, J = 7.7 Hz, 1 H), 8.07 (s, 1 H), 8.14 (d, J = 7.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.9, 31.4, 34.6, 36.7, 41.6, 55.8, 75.6, 79.2, 84.0, 115.2, 121.4, 123.8, 125.9, 128.4, 128.4, 129.3, 129.7, 131.0, 131.3, 133.5, 140.6, 141.5, 156.4, 163.4, 163.5, 165.3; FT-IR (ATR) ν_{max} 3282, 2923, 1787, 1726, 1714, 1632 cm^{-1}; ESI MS (+) ESI (+) 551.2 (M + Na + MeOH) and 567.2 (M + K + MeOH).

General Procedures for Synthesis of Alkoxyamines with Supported Reagent 17. With Betaine Sulfamide. Resin **17** (0.80 mmol/g, 50 mg, 39 μmol) was loaded into a 6 mL SPE cartridge. The resin was suspended in CH_2Cl_2 (5 mL). The SPE cartridge was capped, fixed horizontally onto an orbital shaker and agitated for 1 h. The resin was drained and suspended in CH_2Cl_2. Alcohol (5 equiv) and betaine sulfamide (99 mg, 6 equiv) were added, and the cartridge capped and agitated for 24 h at room temperature. The resin was drained and washed with CH_2Cl_2 (3 × 5 mL), DMF (3 × 5 mL), MeOH (3 × 5 mL), CH_2Cl_2 (5 mL), MeOH (5 mL), and CH_2Cl_2 (5 mL). This resin was then subjected to methylaminolysis.

With Ph_3P/DIAD/Imidazole. Resin **17** (0.80 mmol/g, 50 mg, 39 μmol) was loaded into a 6 mL SPE cartridge. The resin was suspended in CH_2Cl_2 (5 mL). The SPE cartridge was capped, loaded horizontally onto an orbital shaker and agitated for 1 h. The resin was drained and suspended in CH_2Cl_2 (5 mL). Alcohol (5 equiv) and triphenylphosphine (52 mg, 5 equiv) were added, mixed by inverting the cartridge until dissolution and DIAD (39.8 μL, 5 equiv) and imidazole (14 mg, 5 equiv) were added. The cartridge was capped and agitated as previously for 24 h at room temperature. The resin was drained and washed with CH_2Cl_2 (3 × 5 mL), DMF (3 × 5 mL), MeOH (3 × 5 mL), CH_2Cl_2 (5 mL), MeOH (5 mL), and CH_2Cl_2 (5 mL). This resin was then subjected to the cleavage step by methylaminolysis.

With Alkyl Bromides. Resin **17** (0.80 mmol/g, 50 mg, 39 μmol) was loaded into a 6 mL SPE cartridge. The resin was suspended in DMF (5 mL). The SPE cartridge was capped, loaded horizontally onto an orbital shaker, and agitated for 1 h. The resin was drained and suspended in DMF (5 mL). Alkyl bromide (10 equiv) and triethylamine (56.2 μL, 10 equiv) were added. The cartridge was capped and agitated as previously for 24 h at room temperature. The resin was drained and washed with DMF (3 × 5 mL), CH_2Cl_2 (3 × 5 mL), MeOH (3 × 5 mL), CH_2Cl_2 (5 mL), MeOH (5 mL) and CH_2Cl_2 (5 mL). This resin was then subjected to the cleavage step by methylaminolysis.

Cleavage. The resin was suspended in $CHCl_3$-MeOH (9:1, 5 mL), the SPE cartridge was capped, loaded horizontally onto an orbital shaker and agitated for 1 h. The resin was drained, suspended in 5 mL of a 0.05 M methylamine solution in $CHCl_3$−MeOH (9:1, 5 mL), and agitated for 2 h at room temperature. The solution was collected by filtration, the resin was washed with $CHCl_3$ (1 mL) and the filtrate collected and evaporated under reduced pressure (higher than 20 mbar) to afford the O-alkyl hydroxylamine. Yields were determined by NMR titration as described above.

***O*-Alkyl hydroxylamine Analysis.** All the alkoxyamines were analyzed by NMR and GC−MS or HPLC. GC−MS analyses were realized with a solution of the O-alkyl hydroxylamine in MeOH using HP-5 (cross-linked 5% PH ME siloxane, 30 m × 0.32 mm × 0.25 mm) as the stationary phase. Helium flow: 1.5 mL /min. Temperature program: 120 °C for 2min, then 10 °C/min to 280 °C. HPLC separations were performed using an analytical Aquasil-C_{18} column (100 × 3 mm, 3 μm, provided from Thermoelectron) with a flow rate of 0.8 mL

min^{-1}. Detection was at 275 nm for *O*-[(4-nitrophenyl)methyl]-hydroxylamine and at 223 nm for *O*-[(4-methoxyphenyl)ethyl]-hydroxylamine using a photodiode array detector. An isocratic solvent system consisting of (A) acetonitrile and (B) aqueous ammonium acetate buffer (0.1 M pH 6.8) in 10% acetonitrile−90% water was used. Purity and enantiomeric excess of **51** were determined by HPLC using an analytical OD Column (250 × 4.6 mm, 5 μm, provided from Daicel) with a flow rate of 1,0 mL min^{-1} (solvent *i*-PrOH/hexane 8/92). Detection was at 210 nm using a photodiode array detector. The separation of the two enantiomers was verified by co-injection of the racemic compound.

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Supporting Information Available: General experimental procedure; gravimetric titration; NMR titration and Fmoc test; characterization of **9** and **18**−**57**; MAS ^{1}H NMR spectrum of the resins **4a**,**b** and **5**; ^{1}H NMR spectra of **4c**, **9**, **14**, **16**, **18**−**26**, **28**−**32**, **34**−**50**, **52**−**57**, and **59**−**61**; ^{13}C NMR spectra of **4c**, **14**, **16**, **58**, and **61**; GC−MS spectra of **9**, **18**−**37**, **39**−**50**, and **54**−**57**; HPLC spectrum of **51**. This material is available free of charge via the Internet at http://pubs.acs.org.

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