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# A direct functionalization of tertiary alkyl bromides with O-, N-, and C-nucleophiles

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**Abstract**—Silver oxide used in stoichiometric amounts promoted the direct functionalization of *tert*-alkyl bromides and provided the desired adducts in 39–96% isolated yield. Reaction of *tert*-bromides with carboxylic acids yielded esters, with alcohols and phenols yielded alkyl and aryl ethers, with amines and anilines yielded selectively mono-alkylated amines and anilines, and with a C-nucleophile yielded an all-carbon quaternary hydrocarbon. The method was applied to a sequential alkylation of a primary amine with two different alkyl bromides yielding selectively a tertiary amine with three different substituents in one-pot.


While the reactions of primary and secondary alkyl halides with various nucleophiles are among the most employed strategies in organic synthesis, an analogous direct selective functionalization of tertiary alkyl halides remains largely unexplored and certainly underutilized. In addition to inherently poor reactivity of tertiary alkyl halides, reaction selectivity is compromised by the prevalence of the $S_N1$ mechanism, which typically involves a rearrangement of the carbocation intermediates that often yield inseparable mixtures of products. Examples of truly selective direct derivatization of *tert*-alkyl bromides are scarce.[1] To this end, a limited number of reports on direct derivatization of *tert*-alkyl bromides assisted by silver oxide have been reported in the literature; however, the scope has been limited to a handful of closely related examples of a reaction of carboxylic acids and alcohols with tertiary α-bromoamides forming depsipeptides,[2] and α-alkyloxyamides,[3,4] respectively, and a reaction of carboxylic acids with *tert*-butyl bromide forming *tert*-butyl carboxylates.[5]

We became interested in the direct functionalization of *tert*-alkyl halides when faced with the challenge of synthesizing a class of α-(phenyloxy)-α,α-dimethylacetamides (Fig. 1). First, we considered synthetic strategies other than a direct halide displacement. Direct alkylation (method a): while methylation of α-(phenyloxy)-α-methylacetates may be feasible in some cases under forcing conditions, the approach failed for all investigated examples of the general substrate structure depicted in Figure 1. Nucleophilic aromatic substitution ($S_NAr$, method b): aryl fluorides and chlorides reacted with sterically hindered α-hydroxy-α,α-dimethylacetamides but the scope was limited to examples of $R^1$ being a strongly electron-withdrawing group(s) in *p*-position and/or the left-hand side aromatic ring was heterocyclic. This method failed for all other aryl groups, leaving a direct derivatization of *tert*-alkyl halides (method c) as a viable option.

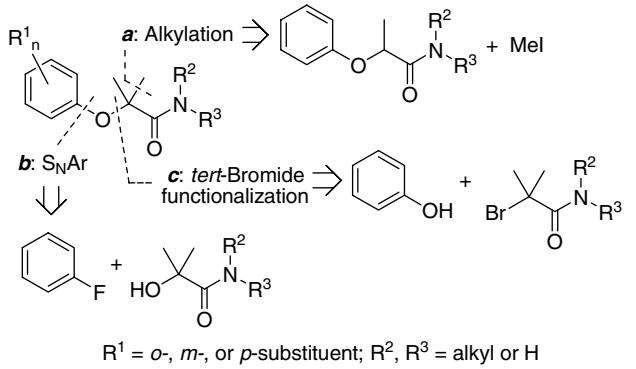


**Figure 1.** Preparation of α-aryloxy-α,α-dimethylacetamides. a: Alkylation of α-aryloxy-α–methylacetamide with methyl halide; b: Nucleophilic aromatic substitution ($S_NAr$) of aryl fluoride or chloride with α-hydroxy-α,α-dimethylacetamides; c: Direct bromide substitution in α-bromo-α,α-dimethylacetamide with phenols.

*Keywords*: Tertiary bromide; Silver oxide; Nucleophile; Steric hindrance; Quaternary.
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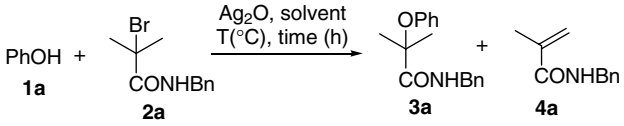
Methods for nucleophilic displacement of tertiary alkyl bromides with phenols using silver oxide in anhydrous acetonitrile, previously published for carboxylic acids and alcohols,[2,3] failed to provide synthetically significant yields of the desired products **3** but rather led to the formation of α-methylacrylamides **4**, the undesired byproducts resulting from HBr elimination (Table 1, entries 1–3). We anticipated that the reaction solvent should play a critical role, regardless whether the bromide displacement proceeds via a charged, partially charged, or radical intermediate. We screened a variety of solvents in a model reaction of phenol **1a** and amide **2a**, including anhydrous DMF, NMP, THF, dichloromethane, ethyl acetate, acetone, toluene, ether, and cyclohexane but found no reaction rate acceleration or selectivity improvement compared to anhydrous acetonitrile (<10% of **3a** was observed by HPLC in each case). The key variable leading to an increased reaction rate turned out to be presence of water in the reaction mixture. When water was used as a co-solvent, a full conversion of **2a** was accomplished within practical reaction time (entries 2 vs 5). In addition, a significant improvement of the ratio of the desired product **3a** versus the undesired **4a** (ratios 3/1 vs 7/1, respectively) was observed as well as an increase in the overall reaction selectivity against other byproducts, which effectively increased the overall yield of the transformation (30% vs 70% for entries 2 vs 5, respectively). The combination of acetonitrile/water in a ratio of 95/5 proved superior to combinations of all other investigated solvents with water (entries 6 vs 7–10) as well as other acetonitrile/water ratios.[6]

The increase in **3a/4a** ratio and the overall reaction selectivity may be explained by a close association of all reaction partners in the key C–O bond forming step in the model reaction of **1a** with **2a**. This would suggest that the silver counter ion may play an important role in the reaction rate and selectivity. The hypothesis proved consistent with the results of an extensive screen of silver salts outlined in Table 2. A panel of silver sources promoted the desired model transformation of **2a** to **3a** with variable rates and degrees of selectivity; in most cases, elimination of HBr from **2a** leading to **4a** represented the major reaction pathway (entries 5-9, 14). No salt provided an advantage over oxide, confirming silver oxide as a superior silver source for both activity and chemo-selectivity (entries 1,2 vs 3–14).

Although conditions for the direct functionalization of *tert*-alkyl bromide were optimized for a single pair of substrates (**1a** and **2a**; Table 1, entry 5), reaction rate and selectivity enhancement allowed for its successful application to a wide range of both nucleophiles (**1**) and electrophiles (Table 3, **2**).

*Carboxylic acids as nucleophiles*: Both aromatic and aliphatic carboxylic acids directly displaced *tert*-alkyl bromide in model electrophile **2a** providing respective esters **3b**–**3h** in good overall isolated yield (Table 3).[7] Although ester formation using silver oxide has been previously reported,[2] the advantage of the partially aqueous conditions reported here is an enhanced rate and higher ratio of the desired **3b** versus the undesired **4a** resulting in higher reaction yield. Compare, for example, data for **3b** in Table 3 versus a ratio of **3b/4a** = 10/1 and 60% isolated yield of **3b** for anhydrous acetonitrile. Although the improvement resulting from water addition may not seem as impressive in the case of **3b**, it is absolutely critical for **3c** and **3h**. While the products are not formed under anhydrous conditions at all, our method provides **3c** and **3h** in excellent yields of 81% and 91%, respectively, despite the extreme steric hindrance of both reactant pairs. Electronic properties of the aromatic ring of nucleophile **1** do not negatively affect the generality of the transformation, for example, electron-deficient **3d** as well as electron-rich **3e**–**g** acids directly displace *tert*-alkyl bromide of **2a** in good yields. Exclusive forma-

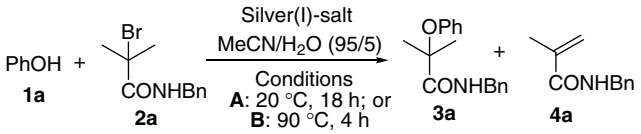
**Table 1.** Optimization of reaction solvent in the displacement of tertiary bromide of a model electrophile **2a** with phenol (**1a**)




| Entry | Solvent | *T* (°C) | Conv. of **2a**,[a] rxn. time | **3a**[b] (%) | **4a**[b] (%) | Other[c] (%)[b] |
|---|---|---|---|---|---|---|
| 1 | MeCN[d] | 20 | 15% in 18 h | 10 | <5 | 5 |
| 2 | MeCN[d] | 20 | 90% in 150 h | 30 | 10 | 40 |
| 3 | MeCN | 90 | 70% in 4 h | 25 | 10 | 35 |
| 4 | MeCN/$H_2O$[e] | 20 | 45% in 18 h | 30 | 5 | 10 |
| 5 | MeCN/$H_2O$[e] | 20 | >90% in 48 h | 70 | 10 | 15 |
| 6 | MeCN/$H_2O$[e] | 90 | >90% in 4 h | 60 | 10 | 15 |
| 7 | Acetone/$H_2O$[e] | 90 | 90% in 4 h | 40 | 15 | 35 |
| 8 | THF/$H_2O$[e] | 90 | 40% in 4 h | 20 | 20 | <5 |
| 9 | DCM/$H_2O$[e] | 90 | 10% in 4 h | 5 | 5 | <5 |
| 10 | DMF/$H_2O$[e] | 90 | 60% in 4 h | <5 | 5 | 30 |

[a] HPLC conversion.
[b] HPLC yield.
[c] Other, unidentified byproducts.
[d] Entries 1 and 2 included for a side-by-side comparison to prior literature reports, see Refs. 2 and 3.
[e] Ratio of organic solvent/water = 95/5 (for other solvent ratios, see Ref. 6).

**Table 2.** Optimization of silver counter ion in the displacement of *tert*-bromide of a model electrophile **2a** with phenol (**1a**)




| Entry | Silver(I)-salt | Rxn cond.[a] | Conv. of **2a**[b] (%) | **3a**[c] (%) | **4a**[c] (%) | Other[d] (%)[c] |
|---|---|---|---|---|---|---|
| 1 | $Ag_2O$ | A | 45 | 30 | 5 | 10 |
| 2 | $Ag_2O$ | B | >90 | 60 | 10 | 15 |
| 3 | $Ag_2S$ | B | 10 | 0 | 5 | 5 |
| 4 | $Ag_2Se$ | B | <5 | 0 | <5 | 0 |
| 5 | $Ag_2CO_3$ | B | 30 | 10 | 10 | 10 |
| 6 | AgOAc | B | 20 | 0 | 20 | 0 |
| 7 | AgOTf | B | 40 | 0 | 40 | 0 |
| 8 | AgOMs | B | >90 | 0 | 90 | 0 |
| 9 | $AgSbF_6$ | B | 20 | 0 | 20 | 0 |
| 10 | AgF | A | 90 | 20 | 5 | 70[e] |
| 11 | $AgHF_2$ | A | >90 | 0 | 10 | 30+50[e] |
| 12 | AgBr | B | 5 | 0 | 5 | 0 |
| 13 | AgI | B | <5 | 0 | <5 | 0 |
| 14 | AgCN | B | 50 | 10 | 40 | 0 |

[a] Reaction conditions, A: 18 h @ 20 °C, or B: 4 h @ 90 °C.
[b] HPLC conversion.
[c] HPLC yield.
[d] Other, unidentified byproducts.
[e] Major product *N*-benzyl α-fluoro-α,α-dimethylacetamide, which resulted from the displacement of bromide with fluoride; this observation is consistent with the literature:[11]

tion of **3f** demonstrates a complete selectivity of bromide displacement with carboxylic acid in the presence of unprotected phenol, which in turn may be subsequently derivatized without protective group manipulation.

*Phenols and alcohols as nucleophiles*: The scope of the nucleophiles amenable to displace *tert*-bromide of **2a** extends beyond carboxylic acids. The formation of aryl ethers **3i**,**j** (Table 3) represents two examples of *p*- and *m*-substituted phenol additions to **2a** (Table 3; for another phenol-derived example, see Table 1, entry 5). Similarly, alcohol derived alkyl ethers exemplified by **3k** are prepared under the same conditions.

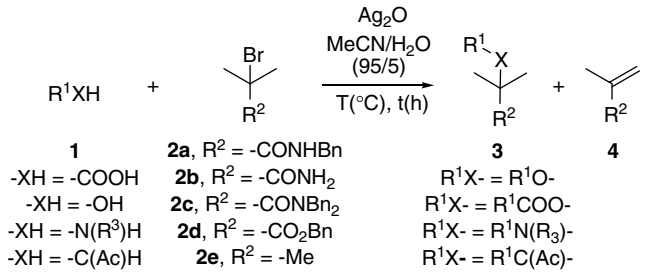
*Amines and anilines as nucleophiles*: Both anilines and primary amines undergo a selective reaction with 1 equiv of **2a** providing exclusively secondary anilines and amines devoid of over-alkylation (**3l**–**n** in Table 3). It is noteworthy that the reaction conditions are so mild that a typically labile boronic acid ester in **3m** remains intact providing an attractive handle for a subsequent product derivatization. An example of a secondary amine also undergoes the direct *tert*-bromide displacement, albeit at elevated temperature, selectively yielding a tertiary amine **3o**.

*C-nucleophile*: An example of a carbon nucleophile (ethyl acetoacetate) directly displacing *tert*-alkyl bromide of **2a** under the method's reaction conditions provided an example of a hydrocarbon bearing an all-carbon quaternary center directly adjacent to an all-carbon tertiary center in **3p** (Table 3).

Benzoic acid was utilized to explore the scope of electrophiles suitable for the transformation. In addition to the model secondary amide **2a**, the *tert*-alkyl bromides of primary (**2b**) and tertiary (**2c**) amides are also displaced with benzoic acid yielding the desired esters **3q** and **3r**, respectively, in yields comparable to the secondary amide **3b** (Table 3). The formation of tertiary amide **3q** is particularly important since authors of previously published silver oxide-utilizing methodology postulated that the reaction was fundamentally limited to protic α-bromoamides (primary and secondary amides).[2b,3b] Not only do aprotic amides readily undergo the transformation under our conditions but the scope extends beyond amides to other electrophiles. Of these, esters are exemplified by the reaction of **2d** to **3s**, which has been prepared in 89% yield. Even a fully unfunctionalized electrophile, *tert*-butyl bromide, underwent the transformation, providing an easy access to *tert*-butyl benzoate (**3t**). When alcohols are used as nucleophiles instead of a carboxylic acid with *tert*-butyl bromide, our method provides a convenient access to synthetically valuable *tert*-butyl ethers derived from primary (**3u**) as well as secondary (**3v**) alcohols. While the use of *tert*-butyl bromide as an electrophile for the formation of *tert*-butyl carboxylates has been previously reported,[5] our method is the first example of a direct synthesis of *tert*-butyl ethers.

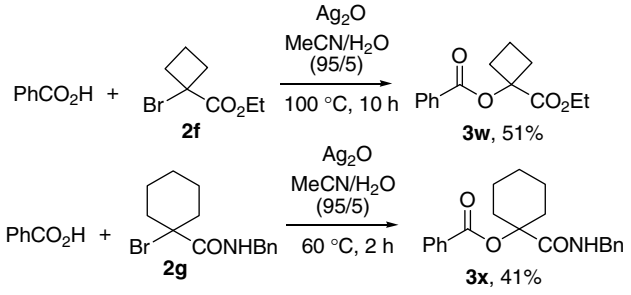
Cyclic *tert*-alkyl bromide electrophiles **2f**,**g** are representatives of additional challenges compared to their acyclic counterparts: **2f** exemplifies a particularly sterically hindered substrate undergoing the reaction with benzoic acid, yielding **3w** in 51% yield (Scheme 1). While the *tert*-alkyl bromide in cyclohexane derivative **2g** is slightly less sterically hindered compared to its cyclobutane analog **2f**, the potential for HBr elimination from **2g** is very high due to the energetically favored

**Table 3.** Substrate scope of the direct functionalization of *tert*-alkyl bromides with O-, N-, and C-nucleophiles




| 3 | $R^1$ | –X– | $R^2$ | $T$ (°C) | $t$ (h) | 3/4[a] | 3[b] (%) |
|---|---|---|---|---|---|---|---|
| **3b** | Ph | –COO– | –CONHBn | 20 | 5 | >50/1 | 74 |
| **3c** | 2,4,6-$Me_3$–$C_6H_2$– | –COO– | –CONHBn | 20 | 2 | 30/1 | 81 |
| **3d** | 4-CN–$C_6H_4$– | –COO– | –CONHBn | 20 | 15 | 40/1 | 70 |
| **3e** | 4-($Me_2N$)-$C_6H_4$– | –COO– | –CONHBn | 60 | 5 | >50/1 | 51 |
| **3f** | 4-HO–$C_6H_4$– | –COO– | –CONHBn | 100 | 2 | >50/1 | 74[c] |
| **3g** | 4-MeO–$C_6H_4$– | –COO– | –CONHBn | 20 | 10 | >50/1 | 70 |
| **3h** | *tert*-Bu– | –COO– | –CONHBn | 20 | 12 | >50/1 | 91 |
| **3i** | 3-Cl–$C_6H_4$– | –O– | –CONHBn | 20 | 15 | >50/1 | 63 |
| **3j** | 4-$CF_3$–$C_6H_4$– | –O– | –CONHBn | 20 | 16 | 30/1 | 72 |
| **3k** | $PhCH_2$– | –O– | –CONHBn | 60 | 4 | 12/1 | 81 |
| **3l** | Ph– | –NH– | –CONHBn | 60 | 5 | >50/1 | 96 |
| **3m** | 4-(4,4,5,5-$Me_4$-1,3,2-dioxaborolan-2-yl)–$C_6H_4$– | –NH– | –CONHBn | 20 | 20 | >50/1 | 55 |
| **3n** | $PhCH_2$– | –NH– | –CONHBn | 20 | 1 | >50/1 | 72 |
| **3o** | $PhCH_2$–(X)–$CH_2Ph$ | –N– | –CONHBn | 60 | 2 | >50/1 | 48 |
| **3p** | Ac-(X)–$CO_2Et$ | –CH– | –CONHBn | 60 | 24 | 8/1 | 39[d] |
| **3q** | Ph– | –COO– | –$CONH_2$ | 20 | 2 | n.d. | 77 |
| **3r** | Ph– | –COO– | –$CONBn_2$ | 60 | 36 | 8/1 | 62 |
| **3s** | Ph– | –COO– | –$CO_2Bn$ | 100 | 24 | 15/1 | 89 |
| **3t** | Ph– | –COO– | –Me | 20 | 2 | n.d. | 73 |
| **3u** | $PhCH_2$– | –O– | –Me | 60 | 4 | n.d. | 61 |
| **3v** | $Ph_2CH$– | –O– | –Me | 60 | 8 | n.d. | 58 |

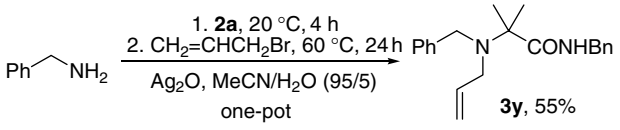
[a] Ratio of **3**/**4** in the crude reaction mixture @ > 95% conversion of **2**.
[b] Isolated yield of analytically pure product **3** (see Supplementary data for full characterization).
[c] Ester as the sole product resulting from selective reaction of the carboxylic acid functionality, no arylether was detected in the crude reaction mixture.
[d] C-alkylation product; approx. 5% of O-alkylated product observed in the crude reaction mixture and separated from the desired C-alkylated product by column chromatography on silica gel.




**Scheme 1.** Direct functionalization of tert-alkyl bromide with benzoic acid: examples of cyclic electrophiles.

endo-ene 1-cyclohexene-1-carboxamide. Even though the elimination of HBr does occur and actually accounts for approximately half of the starting material conversion, the desired ester **3x** is still isolated in a practical 41% yield.

The selectivity observed for the alkylation of primary and secondary amines yielding exclusively secondary and tertiary amines, respectively (**3l**–**o** Table 3), provided a basis for a one-pot tertiary amine synthesis depicted in Scheme 2. Benzylamine was treated with silver oxide and **2a**, the first of two electrophiles. After the first alkylation was completed (in 4 h at 20 °C in this case by LCMS), a second electrophile, allyl bromide, was added to the reaction mixture. After the second alkylation was completed (in 24 h at 60 °C in this case by LCMS), the reaction mixture was simply filtered and purified yielding amine **3y** in 55% overall yield via a single-pot procedure. We believe that this approach represents a particularly attractive facile strategy for the preparation of differentially substituted tertiary amines, which would otherwise require a multi-step synthetic effort and protection group manipulations to avoid bisalkylation with one of the two electrophiles.




**Scheme 2.** One-pot selective formation of tertiary amine bearing three different substituents.

From a mechanistic stand point, it is remarkable that the enormous rate acceleration and increased selectivity for the desired adducts **3** over undesired byproducts **4** reported therein is caused solely by the presence of water in the reaction media (Table 1, entries 1 vs 4). This phenomenon may possibly be explained by the relative increase of the homogeneous character of silver oxide. Although solubility/hydration of silver oxide in aqueous media is low,[8] it generally exceeds the solubility in organic solvents. This may result in an increase in the relative activity of silver oxide due to an increased partition coefficient of silver ions between the liquid versus solid states effectively resulting in the observed rate enhancement.[9] Alternatively, the rate acceleration may be explained by the increased concentration of the free hydroxide anion resulting from the elevated soluability of silver oxide. A free hydroxide anion may increase the nucleophilicity of R–X–H by its partial deprotonation, an idea entertained by kinetic studies of related silver-promoted reactions.[10] This notion would be supported by the failure of alternate silver sources to promote the desired transformation as they could not generate hydroxide anion in solution (Table 2) and explain the selectivity observed for **2f**→**3f** (Table 3). While nucleophile deprotonation may be an important contributing factor to reactions of some R–X–H nucleophiles such as phenols and ethyl acetoacetate, it is unlikely to explain the increased reactivity of others, such as alcohols and amines, for which hydroxide anion is outside of the range needed for any appreciable amount of nucleophile deprotonation. Furthermore, no selectivity for the alkylation of carboxylic group over aniline was observed in case of 4-aminobenzoic acid (such selectivity should be expected based on analogy to **2f**→**3f** should deprotonation be critical). In addition to the rate enhancement of the reaction, an increased selectivity of the reaction in partially aqueous media versus anhydrous conditions is consistent with a tighter association of the silver ion in the bond-forming event of the reaction coordinate either in a transition state or a discrete intermediate complex.

In conclusion, we have identified a general strategy for a direct functionalization of *tert*-alkyl bromides. The method is applicable to a variety of electrophiles including protic and aprotic amides, esters as well as completely unfunctionalized alkyl bromides. These electrophiles undergo a bromide displacement with a wide range of nucleophiles including O-nucleophiles such as carboxylic acids, phenols, and alcohols, N-nucleophiles, such as anilines and amines, and even C-nucleophiles exemplified by ethyl acetoacetate.

## Acknowledgments

The authors would like to gratefully acknowledge Dr. V. Colandrea for valuable discussions and Dr. B. Choi for performing HRMS of compounds **3a**–**3y**.

## Supplementary data

Full experimental procedures and compound characterization by NMR and LCMS, and HRMS analyses; a copy of $^{1}H$ and $^{13}C$ NMR and LCMS is provided for all final compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.06.091.

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6. While the selectivity and the rate of the model reaction remained unchanged with increasing water content, aqueous fraction significantly higher then 5% of the reaction media caused precipitation of **2a** and **3a**. For practical applications, acetonitrile/water ratio of 95/5 proved optimal.
7. A typical experimental procedure: To a mixture of nucleophile **1** (100 mg) and electrophile **2** (0.5 equiv of **2a**–**d** or 4 equiv of **2e**) in acetonitrile (2 mL) and water (0.1 mL), silver oxide (2 equiv) is added in one portion. The resulting heterogeneous reaction mixture is stirred at temperature and for time indicated in Table 3 while monitored by LCMS for conversion of the limiting reagent. The crude reaction mixture is filtered through a disposable frit and solids rinsed with ethyl acetate (2 mL). The combined filtrates are concentrated and subsequently purified either by column chromatography on silica gel (eluent: hexanes/ethyl acetate) or by preparative reverse phase HPLC to afford **3** in isolated yield indicated in Table 3. See the Supplementary data for full experimental details and characterization of all products by $^{1}H$ and $^{13}C$ NMR, LCMS, and HRMS.
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