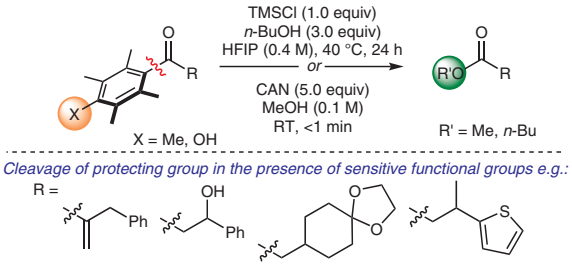
Synlett C. B. Cheong et al. Letter

Pentamethylphenyl (Ph*) and Related Derivatives as Useful Acyl Protecting Groups for Organic Synthesis: A Preliminary Study

Choon Boon Cheong
James R. Frost
Timothy J. Donohoe*

Department of Chemistry, University of Oxford, Chemical Research Laboratory, Mansfield Road, Oxford, OX1 3TA, UK
timothy.donohoe@chem.ox.ac.uk



Received: 13.07.2020
Accepted after revision: 31.08.2020
Published online: 22.09.2020
DOI: 10.1055/s-0040-1707289; Art ID: st-2020-b0396-l

Abstract A study of acyl protecting groups derived from the Ph* motif is reported. While initial studies indicated that a variety of functional groups were not compatible with the Br_2-mediated cleavage conditions required to release the Ph* group, strategies involving the use of different reagents or a modification of Ph* itself (Ph*OH) were investigated to solve this problem.

Key words protecting group, oxidative cleavage, acylium ion, HFIP, deprotection

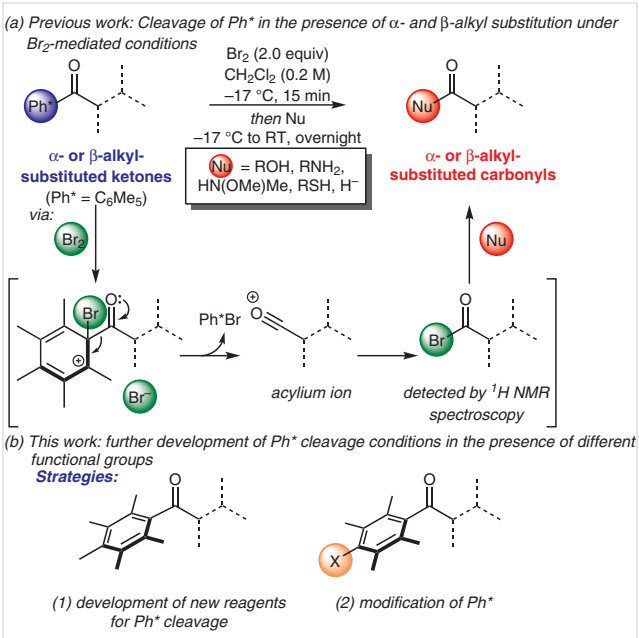
Since their introduction, protecting groups have had a profound impact on the field of organic chemistry, enabling chemists of many disciplines to access complex molecules that were previously out of reach. As a community we now have a range of protecting groups that have been finely tuned for almost any synthetic need, with multiple conditions developed for both their installation and deprotection in the presence of most functional groups.[1] Whilst the primary goal of protecting groups is to prevent one functional group from reacting in preference to another (e.g., an alcohol or amine), they can also influence the stereochemical course of a reaction by steric shielding[2] or neighboring group participation.[3] Depending on the protecting group employed, its synthetically useful migration to an adjacent group,[4] or in rare cases its involvement in new chemical reactions may also occur.[5]

Our recent research has focused on the use of hydrogen-borrowing chemistry for the synthesis of acyclic and cyclic α- and β-branched ketones.[6] This methodology utilized a pentamethylphenyl (Ph*) group, which was key to the success of the reaction. The 2,6-disubstitution pattern of the Ph* group resulted in a 'twisting effect' (compared to the phenyl counterpart), whereby the aromatic ring was twisted out of conjugation with the ketone. This may alleviate steric hinderance around the α-position and enable subsequent aldol reactions. Importantly, the 2,6-disubstitution pattern also shields the carbonyl group from nucleophilic attack, thereby preventing competing 1,2-hydride reduction or self-condensation reactions during the hydrogen-borrowing process, allowing for a clean reaction profile. However, we initially found this group troublesome to remove, with several substrates being impervious to conventional Baeyer–Villiger conditions[7] due to the aforementioned steric shielding of the ketone. We later realized that Br_2 could be used to remove Ph* by means of a retro-Friedel–Crafts acylation *via* a putative acylium ion, which then generated an acid bromide *in situ*. Pleasingly, this acid bromide could be intercepted with a number of different nucleophiles *in situ* to usefully provide a wide range of carbonyl compounds (Scheme 1, a).

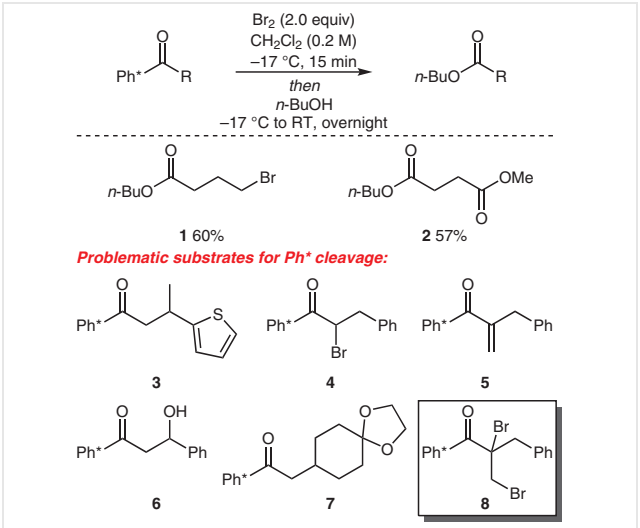
Herein we present our further efforts to investigate the use of Br_2 and also develop alternative conditions for cleavage of the Ph* group. In doing so we also investigated functional group tolerance during Ph* removal, and additional modifications of this new protecting group (Scheme 1, b).

Having previously established that several α- and β-alkylated Ph* ketone substrates could be straightforwardly deprotected with Br_2, we were keen to further study these deprotection conditions. Therefore, we synthesized a small selection of structurally diverse substrates bearing γ-bromo, ester, thiophene, α-bromo, enone, β-hydroxy, and acetal functionalities (Scheme 2). Upon attempted Br_2-mediated cleavage (followed by *in situ* reaction with added *n*-BuOH) the γ-bromo and methyl ester substrates delivered the desired *n*-butyl esters in 60% (**1**) and 57% (**2**) yield, respectively.[8] To our disappointment the remaining functional groups proved incompatible with the Br_2 conditions. α-Brominated substrate **4** was found to be completely unreactive, whilst enone **5** unsurprisingly reacted in preference to

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



Scheme 1 Cleavage of the Ph* group for the synthesis of substituted carbonyl compounds



Scheme 2 Ph*-containing substrates bearing different functional groups and their attempted cleavage using Br_2

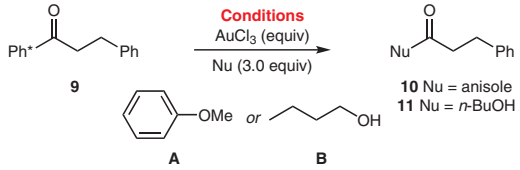
Ph* cleavage, leading to the formation of unwanted dibrominated compound **8** that was similarly unreactive toward Br_2. Compounds containing thiophene (**3**) and β-hydroxy (**6**) motifs resulted in complex mixtures, whilst acetal **7** interestingly gave diastereomeric brominated compounds in which the bromine atom was installed α to the acetal unit (not isolated). This side reaction could have occurred by opening of the acetal and α-bromination of an intermediate enol ether, followed by ring closure. Since it was clear that multiple functional groups were not compatible with the Br_2 conditions as originally reported, we attempted to buffer the reactions using 2,6-lutidine, but this additive completely suppressed Ph* cleavage. As a result, we decided to test alternative conditions for removal of the Ph* group.[9]

Our initial screen focused on previously reported transacylation conditions using model substrate **9** under acidic conditions with either anisole (neat) or *n*-BuOH used to intercept the acylium ion.[10] Whilst this strategy employed undesirable strong acids (neat TfOH) at high temperature, we hoped to find milder alternatives *via* reaction optimization. We established that the desired cleavage reaction (using anisole to give ketone **10**) could be accomplished using a number of strong Brønsted and Lewis acids ($SnCl_4$, $InCl_3$, $AlCl_3$, $BF_3{\cdot}OEt_2$, H_2SO_4, see the Supporting Information (SI)), but were surprised to note that Montmorillonite K10 clay was also effective (see SI). A handful of electrophilic transition metals were also used in stoichiometric quantities ($Pd(OAc)_2$, AgOAc, $Ph_3PAuCl/AgSbF_6$, and $AuCl_3$). Although $Pd(OAc)_2$ and AgOAc proved to be completely ineffective, we were pleased to observe that $Ph_3PAuCl/AbSbF_6$ and $AuCl_3$ provided the product, with the latter affording **10** in 38% isolated yield (see SI). Since $AuCl_3$ has previously been shown to be tolerant of a considerable number of functional groups,[11] we considered this to be an excellent platform for further development.

We continued our study of $AuCl_3$ by lowering the reaction temperature. This proved to be beneficial, with Ph* cleaved from substrate **9** even at room temperature (53%, see Table 1, entries 1–5). We introduced CH_2Cl_2 as a solvent (0.4 M) due to its advantageous solubilizing properties with no detriment to isolated yield (entry 6). At this stage the nucleophile was changed to *n*-BuOH to install an ester functional group following removal of Ph*. However, initial attempts indicated that *n*-BuOH was not compatible with a one-pot procedure (entry 7, no reaction), instead delivering **11** when added to the reaction mixture following 30 min pre-mixing with $AuCl_3$ (entry 8). A further solvent screen (HFIP, THF, PhMe, MeCN, $PhCF_3$, $MeNO_2$, 1,4-dioxane, 1,2-DCE, DME, not shown in Table 1, see SI) revealed that a one-pot procedure could be successful using HFIP (entry 9), providing product **11** in an excellent yield of 92%, albeit with a long reaction time (69 h). All other solvents examined resulted in no desired product, presumably because they could not match HFIP's high polarity and low nucleophilicity.[12] We then looked to make this process catalytic in $AuCl_3$ and so decreased the stoichiometry to 20 mol%. Weak acids (that were previously shown to not cleave Ph*) were also screened to try and affect protodeauration and allow any potential catalytic cycle to turn over. Whilst TFA, NH_4Cl, and SiO_2 provided little or no product (entries 10–12), freshly distilled TMSCl (entry 13) gave **11** in 91% yield. Interestingly, a control experiment whereby $AuCl_3$ was omitted from the reaction media also resulted in Ph* cleavage (entry 14). This result is presumably due to the production of HCl *in situ*.[13] Unfortunately, further attempts to make this process

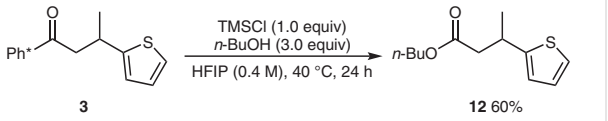
catalytic in $AuCl_3$ were met with failure. Nevertheless, the conditions developed from this study (TMSCl (1.0 equiv), *n*-BuOH, HFIP, RT) were useful, because they proved advantageous for the deprotection of the problematic thiophene-containing substrate **3** (see Schemes 2 and 3). Formation of **12** was found to proceed smoothly at slightly raised temperature (40 °C) in 60% yield over 24 h (Scheme 3).

Table 1 Optimization Conditions for Ph* Cleavage Using $AuCl_3$



Entry	$AuCl_3$ (equiv)	Solvent (0.4 M)	Nu (3 equiv)	Additive (1 equiv)	Temp (°C)	Yield (%)[a]
1	1.2	–	**A**	–	100	38
2	1.2	–	**A**	–	80	38
3	1.2	–	**A**	–	60	45
4	1.2	–	**A**	–	40	52
5	1.2	–	**A**	–	18	53
6	1.2	CH_2Cl_2	**A**	–	18	53
7[b]	1.2	CH_2Cl_2	**B**	–	18	–
8[c]	1.2	CH_2Cl_2	**B**	–	18	ca. 60%[d]
9	1.2	HFIP	**B**	–	18	92
10	0.2	HFIP	**B**	TFA	18	trace
11	0.2	HFIP	**B**	NH_4Cl	18	trace
12	0.2	HFIP	**B**	SiO_2	18	–
13	0.2	HFIP	**B**	TMSCl	18	91
14	–	HFIP	**B**	TMSCl	18	95

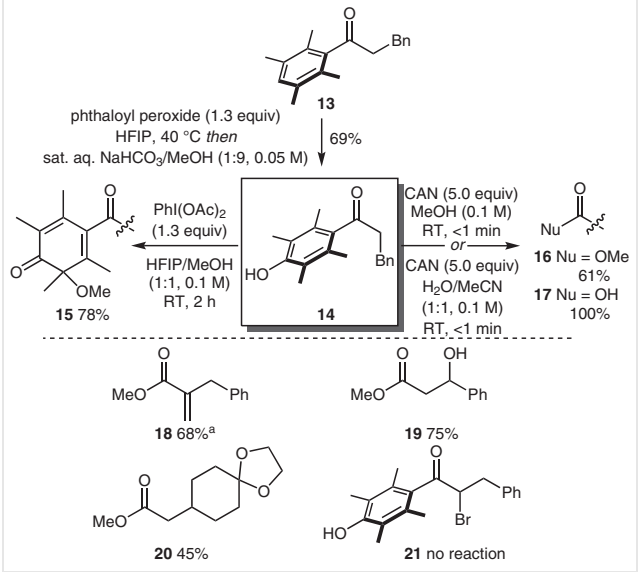
[a] Isolated yield.
[b] No reaction was observed.
[c] Addition of *n*-BuOH after stirring for 30 min.
[d] Approximate conversion by ^{1}H NMR spectroscopy. Reactions carried out using 0.1 mmol of substrate. Reactions in HFIP were stirred at RT for 69 h.



Scheme 3 Removal of Ph* from **3** using TMSCl/HFIP conditions

It was clear to us that although the TMSCl/HFIP reaction conditions were considerably milder than the original starting point (neat TfOH/100 °C), they were still not appropriate for acid-sensitive substrates such as β-hydroxy ketone **6** and acetal-containing compound **7**. Ph* cleavage appears to depend on the introduction of an electrophilic agent, thus we considered that an alternative approach was necessary whereby Ph* itself was modified to increase its reactivity with electrophiles.

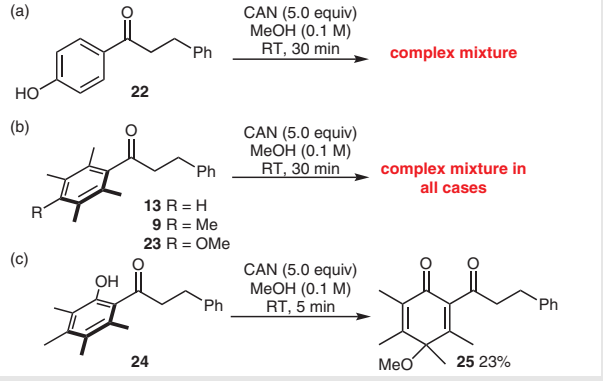
Since phenols are known to undergo several different oxidative dearomatization reactions (e.g., Wessely and related Adler–Becker procedures),[14] we hypothesized that installation of a hydroxy group may be advantageous. In order to maintain the desired twisting effect (imparted by the 2,6-dimethyl substituents), we chose to position the hydroxy group *para* to the acyl unit (**14**). This transformation can be achieved using the peroxide conditions of Siegel in one step from a durene intermediate such as ketone **13** (Scheme 4).[15,16] The search for a suitable oxidant began with PIDA, since hypervalent iodine reagents are often employed in phenol oxidations.[17] Methanol was used as a co-solvent in hope that intermolecular attack would occur at the 4-position (relative to the hydroxy group) and promote ring cleavage. However, the dearomatized 2-substituted product **15** was isolated instead. With this result in mind, we turned our attention to different oxidizing agents. Pleasingly, we discovered that CAN (5.0 equiv) could be used to affect the desired oxidative cleavage transformation. Modification of the co-solvent allowed for the formation of the methyl ester **16** or carboxylic acid **17** in good to excellent yield (Scheme 4).[18] Moreover, the reaction was found to be extremely fast, proceeding to completion in <1 min. Having established this proof of concept, the equivalent hydroxylated variants (Ph*OH) of problematic substrates **4**, **5**, **6**, and **7** were prepared (see SI) and treated under these new conditions. To our delight the corresponding methyl esters **18**, **19**, and **20** were formed in moderate to good yield. This represented a major advance over our previous deprotection



Scheme 4 Cleavage of Ph*OH. [a] Yield determined by ^{1}H NMR spectroscopy as the duroquinone byproduct was inseparable from **18**.

conditions, with Ph*OH providing a complementary approach to substrates that are acid sensitive or incompatible with Br_2 or TMSCl.

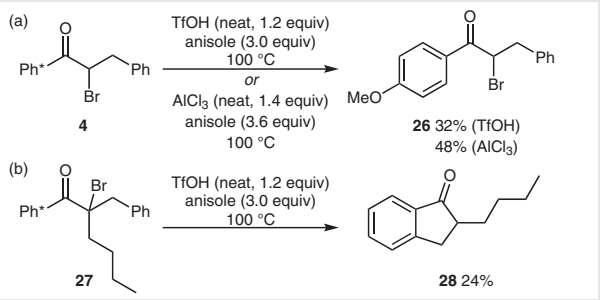
The methyl substituents on **14** were found to be crucial for a clean deprotection reaction (**22**, Scheme 5, a; complex mixture formed), as was the hydroxy group itself (Scheme 5, b) since treatment of the durene precursor **13**, Ph* **9**, and MeO-substituted variant **23** with CAN all resulted in complex mixtures containing no desired product. Installation of the hydroxy group *ortho* to the acyl unit (**24**) was also not productive in so far as dearomatized species **25** was obtained, with multiple other unidentifiable compounds and no cleavage product observed (Scheme 5, c). These control experiments indicated that *para*-hydroxy substitution (Ph*OH) was optimal.



Scheme 5 Further variants and control substrates

Having identified several complementary approaches to our original Br_2-mediated cleavage conditions, we recognized that the presence of an α-electron-withdrawing group was still problematic with respect to arene ring removal (see α-bromo compounds **4** and **21**). We investigated this substrate class further and found that only the most aggressive reaction conditions involving neat TfOH or $AlCl_3$ (1.2–1.4 equiv) at 100 °C in the presence of anisole (3.0–3.6 equiv) resulted in cleavage of the Ph* group and transacylation to give ketone **26** (Scheme 6, a). Next an alkyl chain was installed α to the carbonyl in order to investigate substitution at this position (**27**). However, treatment under TfOH conditions surprisingly resulted in a complex mixture of products instead, the most predominant being literature known debrominated ketone **28**,[19] which is clearly formed by intramolecular trapping of the putative acylium ion (Scheme 6, b). Such reactivity had not been observed in any other cleavage process and may be facilitated by the Thorpe–Ingold effect; and illustrates an alternative reaction manifold during Ph* removal to further explore.

In conclusion, we have presented our preliminary efforts to develop new conditions for the cleavage of the Ph* group. A selection of molecules containing diverse functional groups were synthesized and found not to be compatible with the Br_2-mediated cleavage conditions we reported previously. This led us to investigate the use of different Brønsted and Lewis acids, with TMSCl (1.0 equiv), *n*-BuOH, HFIP, 40 °C being developed as an alternative. In contrast to Br_2, these conditions were found to be compatible with thiophene-containing compound **3**. In the case of compounds **5**, **6**, and **7**, further modification of Ph* was necessary to facilitate its removal. This was achieved by incorporation of a hydroxy group (Ph*OH) and treatment with CAN as an oxidant. Substrates bearing α-bromo substitution continue to be problematic, although Ph* can be cleaved using strongly acidic conditions. Work to further investigate the use of Ph* and its derivatives as a protecting group for organic synthesis remains ongoing in our laboratory.



Scheme 6 Cleavage of Ph* compounds bearing an α-bromo substituent

Funding Information

We are grateful to the A*STAR, Singapore (C.B.C.) and the Engineering and Physical Sciences Research Council [J.R.F. and T.J.D., Established career fellowship (EP/L023121/1)] for generous financial support.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707289.

References and Notes

(1) (a) Kocieński, P. J. *Protecting Groups*; Thieme: Stuttgart, **2003**. (b) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*; Wiley-Interscience: Hoboken, **2006**.
(2) For selected examples of protecting groups influencing the stereochemical course of a reaction, see: (a) Overman, L. E.; McCready, R. J. *Tetrahedron Lett.* **1982**, *23*, 2355. (b) Bols, M.; Pedersen, C. M. *Beilstein J. Org. Chem.* **2017**, *12*, 93.
(3) For selected examples of neighboring group participation, see: (a) Zalewski, Z. S.; Wendler, N. L. *Chem. Int. London* **1975**, 280. Application in the Koenigs–Knorr reaction: (b) Harreus, A.; Kunz, H. *Liebigs Ann. Chem.* **1986**, 717.
(4) For selected examples of protecting group migration, see: (a) Roslund, M. U.; Aitio, O.; Wärna, J.; Maaheimo, H.; Murzin, D. Y.; Leino, R. *J. Am. Chem. Soc.* **2008**, *130*, 8769. (b) Hillier, M. C.; Meyers, A. I. *Tetrahedron Lett.* **2001**, *42*, 5145.

(5) For a selected example whereby the acetate group is involved in a Meyer–Schuster rearrangement, see: Engel, D. A.; Dudley, G. B. *Org. Biomol. Chem.* **2009**, *7*, 4149.
(6) (a) Frost, J. R.; Cheong, C. B.; Akhtar, W. M.; Caputo, D. F. J.; Stevenson, N. G.; Donohoe, T. J. *J. Am. Chem. Soc.* **2015**, *137*, 15664. (b) Akhtar, W. M.; Cheong, C. B.; Frost, J. R.; Christensen, K. E.; Stevenson, N. G.; Donohoe, T. J. *J. Am. Chem. Soc.* **2017**, *139*, 2577. (c) Akhtar, W. M.; Armstrong, R. J.; Frost, J. R.; Stevenson, N. G.; Donohoe, T. J. *J. Am. Chem. Soc.* **2018**, *140*, 11916. (d) Armstrong, R. J.; Akhtar, W. A.; Young, T. A.; Duarte, F.; Donohoe, T. J. *Angew. Chem. Int. Ed.* **2019**, *58*, 12558. (e) Armstrong, R. J.; Akhtar, W. M.; Frost, J. R.; Christensen, K. E.; Stevenson, N. G.; Donohoe, T. J. *Tetrahedron* **2019**, *75*, 130680. (f) Wübbolt, S.; Cheong, C. B.; Frost, J. R.; Christensen, K. E.; Donohoe, T. J. *Angew. Chem. Int. Ed.* **2020**, *59*, 11339.
(7) Baeyer, A.; Villiger, V. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 3625.
(8) (a) For **1** (bromide), see: Mudyiwa, M.; Ndinguri, M. W.; Soper, S. A.; Hammer, R. P. *J. Porphyrins Phthalocyanines* **2010**, *14*, 891. For **2** (methyl ester), see: (b) Jiménez-Rodriguez, C.; Eastham, G. R.; Cole-Hamilton, D. J. *Inorg. Chem. Commun.* **2005**, *8*, 878.
(9) Previous conditions for the cleavage of related (mesityl) functional groups required the use of strong protic acids, see: (a) Schubert, W. M.; Latourette, H. K. *J. Am. Chem. Soc.* **1952**, *74*, 1829. (b) Bender, M. L.; Ladenheim, H.; Chen, M. C. *J. Am. Chem. Soc.* **1961**, *83*, 123. (c) Bender, M. L.; Chen, M. C. *J. Am. Chem. Soc.* **1963**, *85*, 37.
(10) El-Khawaga, A.; Roberts, R.; Sweeney, K. M. *J. Org. Chem.* **1985**, *50*, 2055.
(11) For selected recent reviews on gold catalysis in synthesis, see: (a) Pflästerer, D.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2016**, *45*, 1331. (b) Zi, W.; Toste, F. D. *Chem. Soc. Rev.* **2016**, *45*, 4567. (c) Shahzad, S. A.; Sajid, M. A.; Khan, Z. A.; Canseco-Gonzalez, D. *Synth. Commun.* **2017**, *47*, 735.
(12) For selected reviews on HFIP, see: (a) Bégué, J.; Bonnet-Delpon, D.; Crousse, B. *Synlett* **2004**, 18. (b) Colomer, I.; Chamberlain, A. E. R.; Haughey, M. B.; Donohoe, T. J. *Nat. Rev. Chem.* **2017**, *1*, 88.
(13) A control experiment using TMSCl (2.0 equiv) in CH_2Cl_2 at RT was performed and gave only unreacted starting material.
(14) (a) Wessely, F.; Lauterbach-Keil, G.; Schmid, F. *Monatsh. Chem.* **1950**, *81*, 811. (b) Wessely, F.; Sinwel, F. *Monatsh. Chem.* **1950**, *81*, 1055. (c) Metlesics, W.; Wessely, F.; Budzikiewicz, H. *Monatsh. Chem.* **1958**, *89*, 102. (d) Wessely, F.; Budzikiewicz, H. *Monatsh. Chem.* **1959**, *90*, 62. (e) Adler, E.; Brasen, S.; Miyake, H. *Acta. Chem. Scand.* **1971**, *25*, 2055. (f) Becker, H.-D.; Bremholt, T.; Adler, E. *Tetrahedron Lett.* **1972**, *13*, 4205.
(15) Yuan, C.; Eliasen, A. M.; Camelio, A. M.; Siegel, D. *Nat. Protoc.* **2014**, *9*, 2624.
(16) Ph*OH could also be cleaved using IBr, providing a mixture of phenolic esters as the major product(s). TFA (aq.) was also effective but is quite harsh, whilst methanolic HCl did not cleave Ph*OH at RT (see SI for these examples). These conditions were not investigated further.
(17) Yoshimura, A.; Zhdankin, V. V. *Chem. Rev.* **2016**, *116*, 3328.
(18) **Typical Procedure for CAN-Mediated Cleavage: Synthesis of 16**
To a solution of phenol **14** (28.2 mg, 0.10 mmol) in MeOH (1.0 mL) was titrated a solution of CAN (272 mg, 0.50 mmol) in MeOH (0.5 mL) at RT in the open atmosphere until the color of the CAN solution persisted (orange, typically 4–5 equiv). The reaction mixture was diluted with H_2O (3 mL) and stirred for 5–10 min, then further diluted with CH_2Cl_2 (2 mL), and saturated with NaCl. The layers were separated, the aqueous layer extracted with CH_2Cl_2 (5 × 1.5 mL), the combined organics dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, eluent: pentane–Et_2O, 99:1) afforded ester **16** (10.1 mg, 61%) as a volatile colorless oil. IR (film): ν_{max} = 3087, 3064, 3028, 3002, 2952, 1735, 1604, 1497, 1454, 1436, 1365, 1293, 1255, 1195, 1161, 1079, 1029, 986, 950, 896, 837, 771, 750, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.26 (2 H, m, Ph), 7.25–7.17 (3 H, m, Ph), 3.68 (3 H, s, OCH_3), 3.05–2.90 (2 H, m, CH_2Ph), 2.68–2.58 (2 H, m, CH_2COOCH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.5 (C=O), 140.6 (ArC), 128.6 (2 C, 2 × ArCH), 128.4 (2 C, 2 × ArCH), 126.4 (ArCH), 51.8 (OCH_3), 35.8 (CH_2COOCH_3), 31.1 (CH_2Ph).
(19) Womack, G.; Angeles, J. G.; Fanelli, V. E.; Heyer, C. A. *J. Org. Chem.* **2007**, *72*, 7046.

