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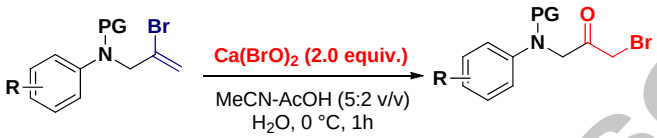

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Chemoselective oxidative hydrolysis of EWG protected α-arylamino vinyl bromides to α-arylamino-α'-bromoacetones.

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ABSTRACT

Vinyl bromides bearing an arylamino group in the vicinal position are chemoselectively transformed into interesting α-arylamino-α'-bromoacetones through a straightforward oxidative hydrolysis promoted by calcium hypobromite under mild acidic conditions. Significantly, this particular combination [vinyl bromides and $Ca(BrO)_2$] avoids bromination at both the aromatic ring and activated positions in groups substituting the amine nitrogen. The usefulness of this class of brominated ketones has been shown in a Wittig homologation.

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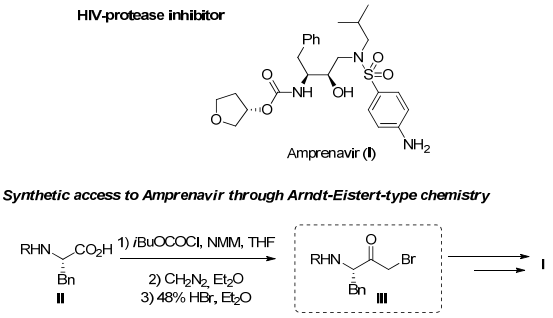
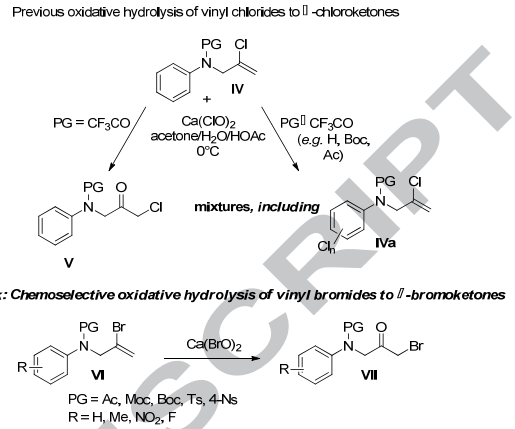
α-Halo carbonyl compounds are versatile building blocks in organic synthesis.[1,2] In fact, the presence of two electrophilic vicinal carbons makes them suitable for reactions with different nucleophiles. In particular, α-bromo derivatives are excellent substrates to carry out nucleophilic displacements (both in synthetic and bio-organic processes) which are often not straightforward when run on chlorinated analogues.[1,3] Moreover, the connection of the α-bromo ketone motif with a substituted amino group at the α'-position turns the resulting structure into a particularly attractive moiety from the perspective of a synthetic medicinal chemist, because of the usefulness of such analogues in the preparation of HIV-protease inhibitors (*e.g.* amprenavir, Scheme 1 - *top*).[4,5] As a consequence of the social relevance of the AIDS disease, the synthesis of these analogues continues to be an attractive field of research. Thus,the quest for safer alternatives to Arndt-Eistert based strategies[6-10] (Scheme 1 – *lower trace*) to access the intermediates α-bromo ketones **III** is urgently demanded by both academia and chemical companies.



Scheme 1. Example of a HIV-protease inhibitor and its synthesis *via* a α-amino-α'-bromo ketone intermediate. NMM = *N*-methylmorpholine

Indeed, these multi-functionalized ketones are very reactive entities because of the well known self-condensation they undergo *via* intermolecular addition of the amino group to the carbonyl.[11,12] As it can be foreseen, this particular behaviour is related to the nitrogen nucleophilicity and thus, the presence of suitable electron-withdrawing groups is pivotal for avoiding any decomposition processes.[13,14] It becomes clear that their effectiveness should be a balance between the capability to stabilize the resulting α-amino-α'-haloketone and the possibility to manipulate them in a chemoselective fashion.

In this regard, in order to circumvent the difficulties of using 1,3-dichloroacetone in nucleophilic displacements,[15] recently our group has reported a series of protocols to access α-arylamino-α'-chloropropan-2-ones (**V**, Scheme 2, *top*) through oxidative hydrolysis of vinyl chlorides with $Ca(ClO)_2$,[16] oxidation of the corresponding chlorohydrins[17] or *via* chloromethylation of Weinreb amides with the carbenoid chloromethyllithium.[18] As a common feature, these procedures are severely affected by the nature of the EWG employed. For instance, the oxidative hydrolysis of vinyl chlorides **IV** could be efficiently used only in the presence of a strongly electron-withdrawing trifluoroacetyl group on the nitrogen atom.[16] This strict requirement is due to the evidence that it is the only one able to suppress any concomitant halogenation of the aromatic ring **IVa** or of potential activated positions (*i.e.* the methyl group of a simple acetamide). In addition, the direct oxidation of bromohydrins is limited by the chemoselective opening of epibromohydrins with an arylamines.[19] Also, the use of the lithium carbenoid strategy can be affected by the high instability of these reagents as pointed out by Köbrich in his pioneering studies.[20]



Scheme 2. Oxidative hydrolysis of vinyl halides to the corresponding α-haloketones.

Therefore, the preparation of α-arylamino-α'-bromopropan-2-ones **VII** has not been addressed yet and, in this Letter, we report a chemoselective and straightforward method via the bromination of *N-(2*-bromoallyl)anilines **VI** with $Ca(BrO)_2$ (Scheme 2, *lower trace*), a mild oxidizing bromonium source recently described in our group for the chemoselective oxidation of allylic sulfides to the corresponding sulfoxides.[21]

As a matter of fact, this work was based on the quest for a masked α-bromoketone functionality that in the presence of a bromonium source would deliver directly the desired α-bromo carbonyl derivative. Evidently, such approach would overcome the chemoselective drawbacks related to multi-chlorinations observed when the reaction was attempted on vinyl chlorides in the presence of hypochlorites.[16]

The starting point for our studies was an easy preparation of the required vinyl bromides through a sequential chemoselective KF-Celite mediated synthesis of *N-(2*-bromoallyl)anilines **1a-j**,[22,23] followed by the introduction of various *N*-EWGs *via* CaO-acylation with acid chlorides to obtain the corresponding disubstituted vinyl bromides **2a-h**[24] *or via* the reaction with Boc_2O in EtOH[25] for compounds **2i-j** (Scheme 3 – *via a*). Interestingly, *N*-tosyl- and *N*-(4-nosyl) - protected vinyl bromides **2k** and **2l** were prepared in one step from *N*-tosyl-type anilines and 2,3-dibromopropene in the presence of KF-Celite (Scheme 3 – *via b*).

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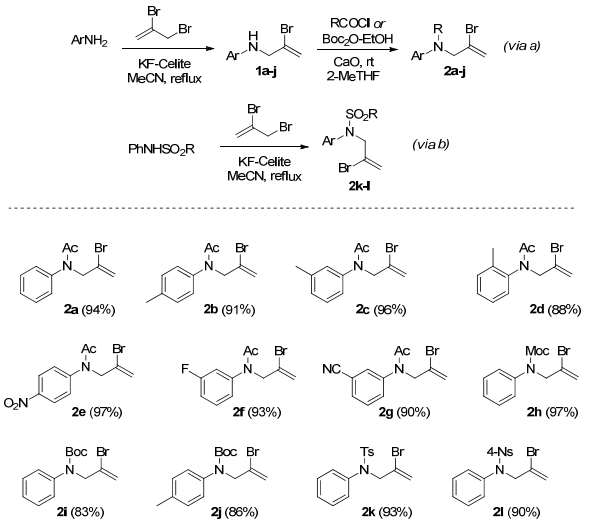
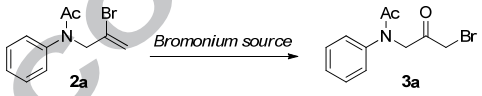


Scheme 3. Preparation of the *N*-EWGs protected vinyl bromides.

Thus, with the *N*-(2-bromoallyl)-*N*-protected anilines series in hand, we turned our attention to their chemoselective oxidative bromination into the corresponding α-bromo ketones, leaving the aromatic and the *N*-acyl moieties untouched.

The reaction of *N*-(2-bromoallyl)-*N*-acetylaniline **2a** was selected as the model reaction, bearing in mind that the analogous transformation carried out on the corresponding chlorocompounds in the presence of NaClO or $Ca(ClO)_2$ gave a mixture of chlorinated compounds both on the aromatic ring and on the amidic methyl group.[16] As shown in Table 1, a brief screening of various brominating agents revealed that $Ca(BrO)_2$ was the best one compared to NaBrO[26] or NBS[27,28] (entries 1-3). By increasing the loading of the hypobromite from 1.0 equiv. to 2.0 equiv. (entry 4), it was possible to obtain **3a** in 85% isolated yield. The choice of the solvent was important in order to obtain satisfactory results: polar aprotic solvents (entries 4-6, 8), as a consequence of their complete miscibility with water, have a beneficial effect compared to apolar ones (entries 9-10), being acetonitrile the preferred medium (entries 5-6).

Table 1. Oxidative hydrolysis of the *N*-EWGs protected vinyl bromides: reaction optimization.



Entry	Oxidant (equiv.)	Solvent	Acid[a]	Temp. (ºC)	Reaction Time (h)	Yield of **3a** (%)[b]
1	NaBrO (1.0)	Acetone	AcOH	0	1	75
2	NBS (1.0)	Acetone	AcOH	0	1	68
3	$Ca(BrO)_2$ (1.0)	Acetone	AcOH	0	1	79
4	$Ca(BrO)_2$ (2.0)	Acetone	AcOH	0	1	85
5	$Ca(BrO)_2$ (2.0)	CH_3CN	AcOH	0	1	91
6	$Ca(BrO)_2$ (2.0)	CH_3CN	HBr[b]	0	1	89
7	$Ca(BrO)_2$ (2.0)	CH_3CN	--	0	24	18
8	$Ca(BrO)_2$ (2.0)	DMSO	AcOH	0	1	84
9	$Ca(BrO)_2$ (2.0)	CH_2Cl_2	AcOH	0	1	42
10	$Ca(BrO)_2$ (2.0)	Benzene	AcOH	0	1	30
11[d]	$Ca(BrO)_2$ (2.0)	CH_3CN	AcOH	20	1	62
12	$Ca(BrO)_2$ (2.0)	CH_3CN	AcOH	-20	24	52

[a] 5:2 v/v mixture of solvent and acid, respectively. [b] Isolated yields. [c] 5 mol %.

Significantly, by increasing the temperature from 0 °C to 20 °C (entry 11) showed a deleterious effect on the overall transformation. On the contrary, running the reaction at -20 °C (entry 12) implies a conspicuous increasing of the time. It is worth stressing the importance of performing reactions in the presence of AcOH or a different protic acid (HBr, entry 6) as a consequence of its capability to properly deliver the active bromonium through the modification of the equilibria existing within the brominated species (BrO^-, Br^-, HBrO). Evidently, the use of AcOH is preferred (over HBr) because of its mildness and potential use to apply the method to acid-sensitive substrates. Thus, in the absence of protic acids, the conversion of **2a** was extremely sluggish, being it substantially recovered even after 24 h (entry 7).

This optimization study clearly pointed out that the use of a vinyl bromide as a masked α-bromocarbonyl functionality is advantageous compared to vinyl chlorides which, as stressed above, undergo undesired chlorinations within the molecules skeleton.

In order to study the scope of the reaction, the series of the above prepared vinyl bromides **2b-l**, containing various substituents both on the aromatic ring and on the nitrogen atom were tested under the established reaction conditions. As shown in Scheme 4, the reaction is quite general and chemoselectivity was observed in all cases. The procedure tolerates the presence of reactive substituents towards the generated electrophilic bromonium such as the methyl group on the aromatic rings (**3b-d**, **3j**): no concomitant bromination was detected at all. Interestingly, also nitro (**3e**), cyano (**3g**) and fluorine substituents (**3f**) were well tolerated. Of particular relevance is the complete chemoselectivity observed in the presence of different *N*-substituents: in contrast to the strict needing of using a strong EWG (*i.e.* trifluoroacetyl) in the oxidative chlorination of vinyl chlorides,[16] herein carbamates (**3h-j**), amide (**3b-d**, **3f**) and tosyl-type substrates (**3k-l**) could be successfully employed. It is worth highlighting the mildness of using $Ca(BrO)_2$ compared to $Ca(ClO)_2$: the latter, as we previously found, was able to chlorinate the aromatic ring

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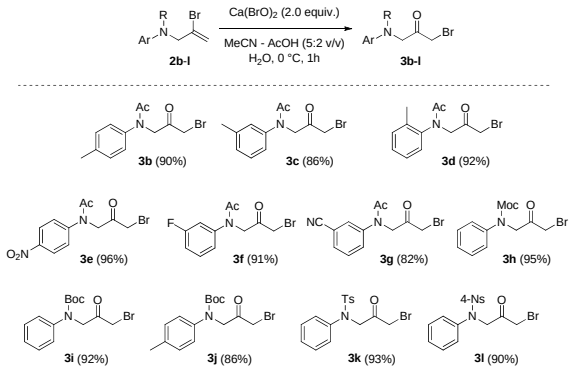
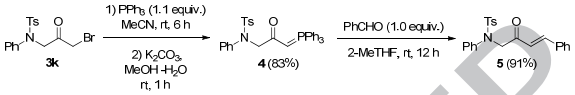
even in the case of a *N*-Boc protected vinyl chloride. Analogously, the methyl group of the tosyl derivative **3k** remained unaffected after the calcium hypobromite treatment.



Scheme 4. Scope of the reaction: synthesis of variously functionalized α-arylamino-α'-bromoacetones.

To demonstrate the synthetic versatility of the prepared α-bromoketones, we reacted tosyl derivative **3k** with PPh_3, followed by basic aqueous treatment to afford the phosphorane **4** in high yield. Subsequently, this phosphorous ylide was employed in a Wittig reaction[29] carried out in the biosolvent 2-MeTHF[30,31] with benzaldehyde to provide the interesting α,β-unsaturated-α'-anilinoketone **5**. (Scheme 5)



Scheme 5. Synthetic versatility of an α-arylamino-α'-bromoacetones in a Wittig homologation.

To conclude, we showed that easily prepared *N*-(2-bromoallyl)-*N*-EWGs substituted anilines represent excellent starting materials for the chemoselective synthesis of α-arylamino-α'-bromoacetones through a simple oxidative hydrolysis of the bromovinyl moiety in the presence of $Ca(BrO)_2$ under mildly acidic conditions. Importantly, the combined use of vinyl bromides and $Ca(BrO)_2$ allows to overcome the multi-chlorinations experimentally observed in analogous processes involving vinyl chlorides and a chloronium source. The high reactivity of a α-bromoketone has been successfully exploited in a Wittig homologation with an aromatic aldehyde to access a functionalized α,β-unsaturated aminoketone.

Representative procedure.

To a solution of the vinyl bromide (1.0 equiv.) in acetonitrile (10 mL) – acetic acid (4 mL) cooled at 0ºC was added $Ca(OBr)_2$ (0.33 M, 2.00 equiv.). The solution was stirred for 1 h at 0ºC and, after the completion indicated by TLC it was poured into a saturated solution of $NaHCO_3$ and extracted with dichlorometane (20 mL x 3). The combined organic phases were dried with anhydrous $MgSO_4$ and the solvent were removed *in vacuo*. Whenever necessary, the crude mixtures were purified by LC to obtain analytical pure sample of bromoketones.

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References.

1. De Kimpe, N.; Verhé, R. In *The Chemistry of α-Haloketones, α-Haloaldehydes and α-Haloimines;* Patai, S. Ed.; Wiley: Chichester, 1988; pp. 1-119.
2. Suffert, J. *Science of Synthesis* **2005,** *26*, 877-904.
3. Pace, V.; Castoldi, L.; Pregnolato, M. *Mini-Rev. Med. Chem.* **2013,** *in press*, Ref. BSP-MRMC-2012-38.
4. Reeder, M. R.; Anderson, R. M. *Chem. Rev.* **2006,** *106*, 2828-2842.
5. Izawa, K.; Onishi, T. *Chem. Rev.* **2006,** *106*, 2811-2827.
6. Arndt, F.; Eistert, B. *Ber. Dtsch. Chem. Ges.* **1935,** *68*, 200-208.
7. Ye, T.; McKervey, M. A. *Chem. Rev.* **1994,** *94*, 1091-1160.
8. Maas, G. *Angew. Chem. Int. Ed.* **2009,** *48*, 8186-8195.
9. Pace, V.; Verniest, G.; Sinisterra, J. V.; Alcántara, A. R.; De Kimpe, N. *J. Org. Chem.* **2010,** *75*, 5760-5763.
10. Rotella, D. P. *Tetrahedron Lett.* **1995,** *36*, 5453-5456.
11. Baktharaman, S.; Hili, R.; Yudin, A. K. *Aldrichim. Acta* **2008,** *41*, 109-119.
12. Concellón, J. M.; Rodríguez-Solla, H. *Curr. Org. Chem.* **2008,** *12*, 524-543.
13. Myers, A. G.; Barbay, J. K. *Org. Lett.* **2001,** *3*, 425-428.
14. Pace, V.; Holzer, W. *Tetrahedron Lett.* **2012,** *53*, 5106-5109.
15. Pace, V. *Synlett* **2010**, 2825-2826.
16. Pace, V.; Martínez, F.; Fernández, M.; Sinisterra, J. V.; Alcántara, A. R. *Adv. Synth. Cat.* **2009,** *351*, 3199-3206.
17. Pace, V.; Cortés-Cabrera, Á.; Fernández, M.; Sinisterra, J. V.; Alcántara, A. R. *Synthesis* **2010**, 3545-3555.
18. Pace, V.; Holzer, W.; Verniest, G.; Alcántara, A. R.; De Kimpe, N. *Adv. Synth. Catal.* **2013,** *355*, 919-926.
19. Singh, G. S.; Mollet, K.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2013,** *113*, 1441-1498.
20. Köbrich, G.; Akhtar, A.; Ansari, F.; Breckoff, W. E.; Büttner, H.; Drischel, W.; Fischer, R. H.; Flory, K.; Fröhlich, H.; Goyert, W.; Heinemann, H.; Hornke, I.; Merkle, H. R.; Trapp, H.; Zündorf, W. *Angew. Chem. Int. Ed.* **1967,** *6*, 41-52.
21. Pace, V.; Castoldi, L.; Holzer, W. *Tetrahedron Lett.* **2012,** *53*, 967-972.
22. Pace, V.; Martínez, F.; Fernández, M.; Sinisterra, J. V.; Alcántara, A. R. *Org. Lett.* **2007,** *9*, 2661-2664.
23. Pace, V.; Sinisterra, J. V.; Alcántara, A. R. *Curr. Org. Chem.* **2010,** *14*, 2384-2408.
24. Pace, V.; Hoyos, P.; Alcántara, A. R.; Holzer, W. *ChemSusChem* **2013,** *6*, 905-910.
25. Vilaivan, T. *Tetrahedron Lett.* **2006,** *47*, 6739-6742.
26. VanBrunt, M. P.; Ambenge, R. O.; Weinreb, S. M. *J. Org. Chem.* **2003,** *68*, 3323-3326.
27. Leanna, M. R.; Morton, H. E. *Tetrahedron Lett.* **1993,** *34*, 4485-4488.

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28. Morton, H. E.; Leanna, M. R. *Tetrahedron Lett.* **1993,** *34*, 4481-4484.
29. Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989,** *89*, 863-927.
30. Pace, V. *Aust. J. Chem.* **2012,** *65*, 301-302.
31. Pace, V.; Hoyos, P.; Castoldi, L.; Domínguez de María, P.; Alcántara, A. R. *ChemSusChem* **2012,** *5*, 1369-1379.

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