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One-Pot Hydroxy Group Activation/Carbon-Carbon Bond Forming Sequence Using a Brønsted Base/Brønsted Acid System

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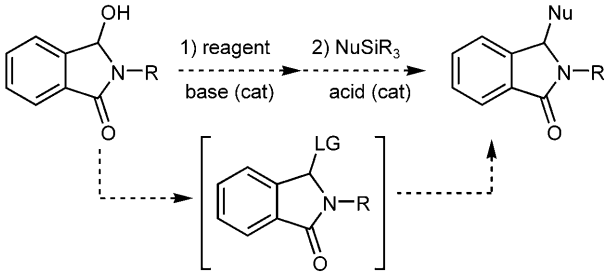
Abstract: A new sequential two-step multicatalytic strategy is presented consisting in the efficient DBU-catalysed trichloroacetimidation of an alcohol followed by a ditriflylamine (Tf_2NH)-catalysed intermolecular alkylation by silicon-based nucleophiles and C–H nucleophiles. The distinct feature of the trichloroacetimidate group allows use of weaker acid catalysts such as 1,1′-bi-2-naphthol (BINOL)-derived phosphoric acid, pointing out the possible development of an enantioselective variant. This unprecedented sequential one-pot Brønsted base-Brønsted acid catalysis further expands the synthetic scope of the trichloroacetimidate group.

Keywords: *N*-acyliminium; alkylation; electrophilic alcohols; sequential organocatalysis; trichloroacetimidates

Due to some specific attributes including good availability and minimum side-products, π-alcohols are ideal electrophilic reagents in modern acid-catalysed alkylative chemistry. Therefore, considerable advances in their Lewis and Brønsted acid-catalysed direct alkylation with carbon nucleophiles have been recently achieved.[1] Because of the poor leaving group ability of the hydroxy group, sometimes even under acid-catalysed conditions, high temperatures and/or long reaction times are frequently required to achieve these reactions with good efficiency. This makes particularly challenging the alkylation of sensitive nucleophiles such as enoxysilanes and ketene silyl acetals, which do not survive under these drastic reaction conditions. Given the greater catalytic activities generally observed in the acid-catalysed alkylation of the more electrophilic acetate derivatives, the latter constitute the common alternative to circumvent the problematic catalytic alkylation of silicon-based nucleophiles. However, the two acylative and alkylative processes are always performed sequentially.[2] Instead, the development of an efficient and reliable tandem reaction sequence combining the installation of a leaving group and its subsequent displacement in a one-pot operation would obviously provide a useful and straightforward novel solution in catalytic alkylative chemistry.

Hydroxy lactams derived from phthalimide and benzhydrol are typical examples of such weakly reactive alcohols in acid-catalysed alkylation with silicon-based nucleophiles.[3] We report herein the efficient alkylation of these model substrates by means of a one-pot homogeneous Brønsted base/Brønsted acid (BB/BA) organocatalytic sequence. According to our strategy, the OH group needs to be *in situ* activated as a transient good leaving group under conditions compatible with the subsequent one-pot catalytic alkylation step (Scheme 1).[4]

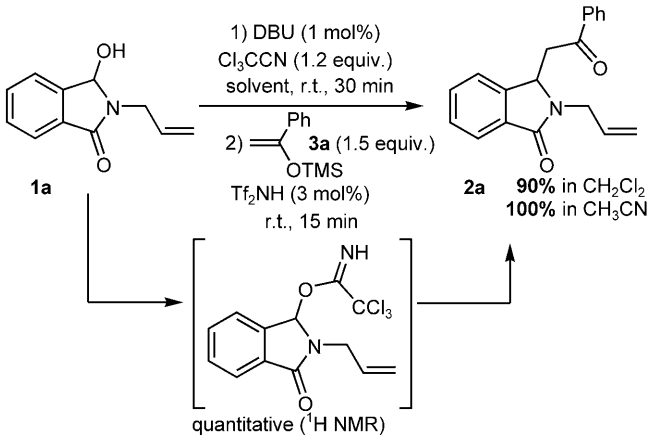


Scheme 1. Objective: sequential one-pot Brønsted base-catalysed hydroxy group activation/Brønsted acid-catalysed nucleophilic displacement.

The trichloroacetimidate group, which is readily generated through the base-catalysed reaction of commercially available trichloroacetonitrile and an alcohol, is a widely used leaving group in cationic chemistry. This chemical group was introduced by Schmidt and co-workers in sugar chemistry and has been found very useful for the development of stereoselective glycosylations under unprecedented mild TMSOTf-catalysed conditions.[5] The unique ability of a sugar-derived trichloroacetimidate to undergo efficient glycosylation processes under mild acidic conditions is obviously due to its specific feature to release neutral trichloroacetamide, which does not interfere with the subsequent catalytic glycosylation. The trichloroacetimidate method has also been useful in carbon-carbon bond forming reactions, with some recent applications to the catalytic alkylation of hydroxy lactams,[6] hydroxymethylimides[7] and benzylic/propargylic type alcohols.[8] However, a two step-two stage protocol was systematically followed in these approaches. Due to its unique features we believe that this trichloroacetimidate chemistry holds the potential for implementing our required BB/BA alkylative organocatalytic sequence.

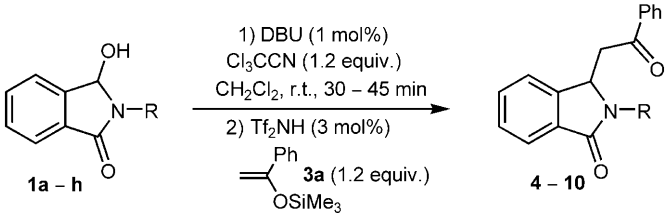
Recognising that the trichloroacetimidation of alcohols generally requires sub-stoichiometric amounts of base (frequently 0.5 equiv. DBU or NaH) and/or large excess (5–10 equiv.) of trichloroacetonitrile, our studies started with the search for optimal catalytic trichloroacetimidation conditions. Starting with compound **1a** (R = allyl), this was efficiently achieved using only 1 mol% DBU and 1.2 equiv. of trichloroacetonitrile in either acetonitrile, dichloromethane or toluene (Scheme 2).[9]

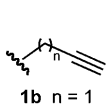
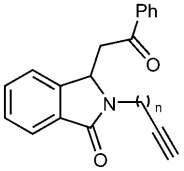
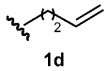
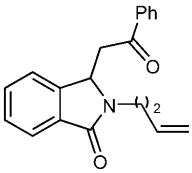
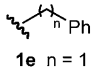
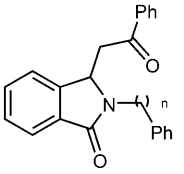
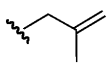
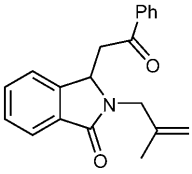
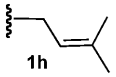
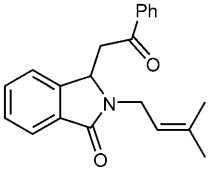
We believe that this careful optimisation not only was crucial for the success of the subsequent acid-catalysed alkylation, but also constitutes the most efficient protocol so far reported for the trichloroacetimidation of a hydroxy group.[10] The subsequent alkylative step was then undertaken in the same reaction vessel. Consecutive addition of trimethylsilyl enol ether derived from acetophenone and only 3 mol% of Tf_2NH[11] readily accomplished the alkylation furnishing the desired Mannich adduct **2a** in yields exceeding 90%. A loading of 3 mol% Tf_2NH was introduced here to ensure entire DBU neutralisation.[12] Careful monitoring of the alkylation step revealed a complete conversion within less than 15 min, confirming the excellent potential of Tf_2NH as pre-catalyst in the catalytic alkylative reactions of silyl enol ethers



Scheme 2. Optimisation of the sequential one-pot Brønsted base-catalysed hydroxy trichloroacetimidation/Tf_2NH-catalysed nucleophilic displacement.

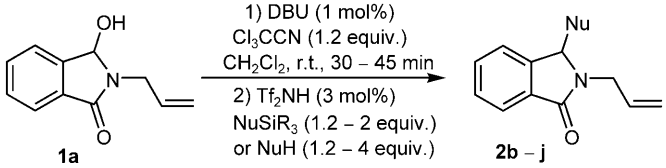
Table 1. Scope of the one-pot BB/BA-catalysed α-amidoalkylation with *N*-protected hydroxy lactams and trimethylsilyl enol ether **3a**.[a]



Entry	Substrate	Product		Yield
1	 **1b** n = 1 **1c** n = 2		**4** n = 1 **5** n = 2	82% 100%
2	 **1d**		**6**	90%
3	 **1e** n = 1 **1f** n = 2		**7** n = 1 **8** n = 2	98% 91%
4	 **1g**		**9**	97%
5	 **1h**		**10**	98%

[a] Experimental details are given in the Supporting Information.

Table 2. Scope of the one-pot BB/BA-catalysed α-amidoalkylation of hydroxy lactam **1a** with various nucleophiles.[a]



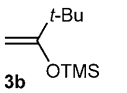
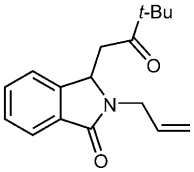
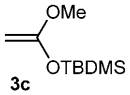
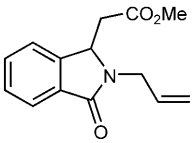
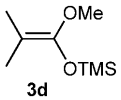
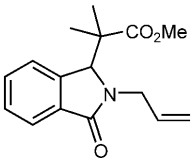
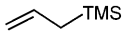
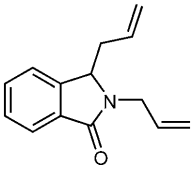
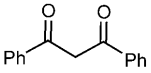
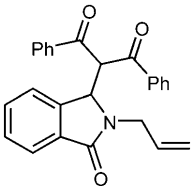
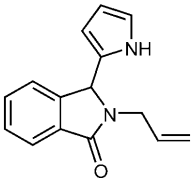
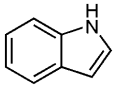
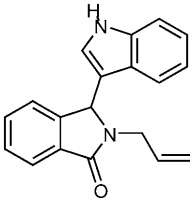
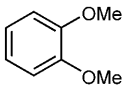
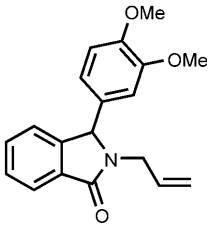
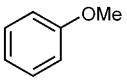
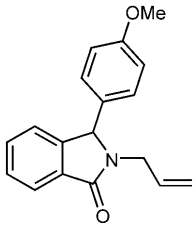
Entry	Nucleophile	Product		Yield
1	 3b		**2b**	76%
2	 3c		**2c**	62%
3	 3d		**2d**	100%
4	 3e		**2e**	96%
5	 11		**2f**	76%[b]
6	 12		**2g**	92%[b]
7	 13		**2h**	100%[b]
8	 14		**2i**	58%[c]

Table 2. (Continued)

Entry	Nucleophile	Product		Yield
9	 15		**2j**[d]	55%[b,e]

[a] Experimental details are given in the Supporting Information.
[b] Reaction carried out in CH_3CN.
[c] 90% corrected yield (calculated from recovered hydroxy lactam).
[d] Isolated with minor by-products as an inseparable mixture.
[e] Estimated yield.

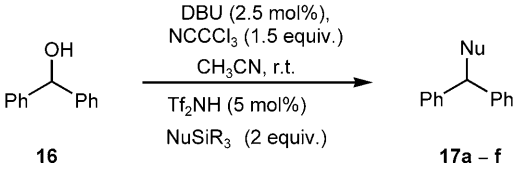
(Scheme 2).[11] To the best of our knowledge, this sequence is the first example of two consecutive chemical transformations distinctly catalysed by a Brønsted base and a Brønsted acid in a homogeneous manner.[13]

The substrate scope of this sequential BB/BA reaction was first examined with silylated enol ether **3a** using a variety of nitrogen substituents on the hydroxy lactam partner (Table 1). In all cases, the reactions proceeded smoothly providing the corresponding alkylation products **4**–**10** in high yields (up to 100%). Reaction producing **8** is noteworthy since the product arising from the potentially undesirable intramolecular Friedel–Crafts reaction was not formed.[14]

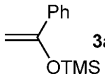
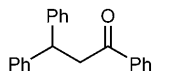
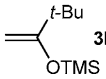
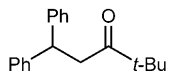
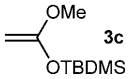
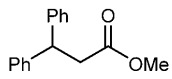
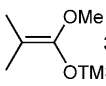
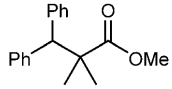
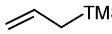
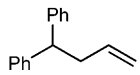
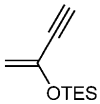
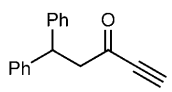
In order to further demonstrate the versatility of this methodology, a series of nucleophiles was tested in the alkylation of hydroxy lactam **1a** using the optimal conditions described above (Table 2).

Most of these reactions were carried out in CH_2Cl_2, but some examples are described in CH_3CN simply to demonstrate that the process tolerates either solvent. When allyltrimethylsilane or silyl enolates derived from pivalone, methyl acetate and methyl 2-methylpropionate were used, the resulting alkylated products **2b–e** were isolated in good to excellent yields (Table 2, entries 1–4).[15] As anticipated from their high reactivity in direct alkylation with hydroxy lactams,[16] typical C–H nucleophiles such as pyrrole and indole were found to be efficient partners in this BB/BA tandem alkylation furnishing adducts **2g** (one regioisomer) and **2h** in high yields (entries 5–7). A major significance of this trichloroacetimidation-based methodology was next demonstrated using less reactive dibenzoylmethane, 1,2-dimethoxybenzene and anisole. Indeed, we were particularly pleased to observe formation of the corresponding Friedel–Crafts adducts **2f** (76%), **2i** (58%) and **2j** (55%)[17]

Table 3. One-pot BB/BA-catalysed alkylation of benzhydrol **17**.[a]



16 **17a – f**

Entry	$NuSiR_3$	Product		Yield[b]
1	 **3a**		**17a**	100%
2	 **3b**		**17b**	84%
3	 **3c**		**17c**	87%
4	 **3d**		**17d**	96%
5	 **3e**		**17e**	97%
6	 **3f**		**17f**	98%

[a] Experimental details are given in the Supporting Information.
[b] Isolated yields.

(entries 8 and 9), while no reactivity was initially observed in direct addition onto hydroxy lactam **1a**.

We next investigated whether this sequential BB/BA catalysis sequence could be extended to common π-alcohols which were previously identified as reluctant substrates under mild Tf_2NH-catalyzed (1–5 mol%) alkylation mode.[3]

Preliminary results using benzhydrol **16** for direct alkylation with silicon-based nucleophiles are presented in Table 3, showing that this kind of alcohol is also a viable candidate. These results further exemplified the synthetic potential of our method since all the alkylated products were obtained in excellent yields (up to 100%).

Finally, we were wondering whether this trichloroacetimidation-based strategy could accommodate weaker Brønsted acid catalysts such as phosphoric acid derivatives, as these would further enable evaluation of an enantioselective process through *in situ* generation of *N*-acyliminium-chiral phosphate ion pair.[18]

rac-BINOL-derived Brønsted acids $\mathbf{PA_{I-III}}$ were then tested in the Mannich reaction of the trichloroacetimidate derived from hydroxy lactam **1a** with silylated enol ether **3a** (Table 4). We were delighted to find that *rac*-BINOL-derived phosphoric acid $\mathbf{PA_I}$[19] or its slightly more acidic dithio analogue $\mathbf{PA_{II}}$[20] (3 mol%) were effective catalysts for the process (Table 4), with $\mathbf{PA_I}$ performing better than the thio analogue $\mathbf{PA_{II}}$ (entries 1–3). These are the first examples documenting the use of phosphoric acid catalysts for the nucleophilic substitution of cyclic N,O-acetals.[21] When the sequential trichloroacetimidation method was performed with Yamamoto's more acidic *N*-triflylphosphoramide catalyst $\mathbf{PA_{III}}$,[22] the resulting alkylated product **2a** was isolated in high yields using either CH_3CN or CH_2Cl_2, (entries 4 and 5). CH_2Cl_2 being a suitable solvent for catalytic enantioselective ion-pairing approaches, we believe that this last finding provides the foundation for the design of a catalytic enantioselective α-amidoalkylation between hydroxy lactams and silyl enol ethers. The efficiency of our trichloroacetimidation-based method was further highlighted by comparison with the direct Mannich reaction starting from the acetoxy lactam derivatives **18**.[23] Whereas use of $\mathbf{PA_I}$ and $\mathbf{PA_{II}}$ completely failed to produce the desired alkylated product (entries 6 and 7), $\mathbf{PA_{III}}$-catalyzed reaction proceeded with high efficiency but only in CH_3CN (entry 8).[24] Indeed, when the reaction was performed in CH_2Cl_2, no reactivity was observed (entry 9).

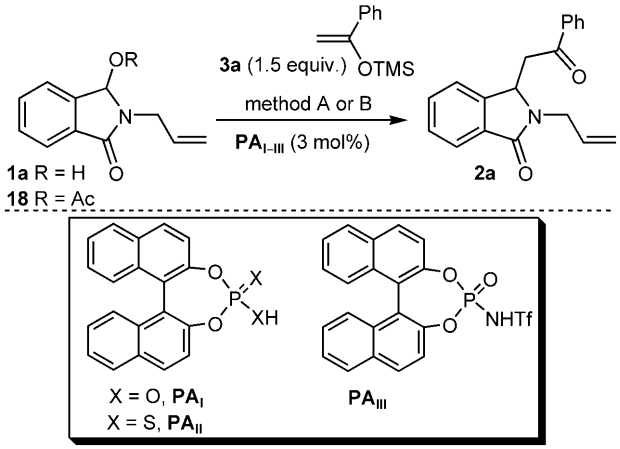
The development of an asymmetric approach using a trichloroacetimidate intermediate is now being investigated and results will be reported in due course.

To summarise, we have developed an original homogeneous nucleophilic substitution using Brønsted base/Brønsted acid (BB/BA) multicatalytic sequence. This very fast room temperature one-pot two stage protocol proceeds through the activation of a hydroxy group *via* a DBU-catalysed trichloroacetimidation step immediately followed by an acid-catalysed nucleophilic displacement of the trichloroacetimidate group. The procedure was established with the nucleophilic substitution of hydroxy lactams and benzhydrol, two weakly reactive alcohols in the direct acid-catalysed alkylation with silyl enol ethers, and was carried out with low catalyst loadings. With few exceptions, all the reactions presented in this report did not proceed if the trichloroacetimidation step was omitted. Besides its synthetic utility in catalytic alkylative chemistry, this simple reaction adds to the increasingly wider repertoire of multicatalytic reactions, delineates new frontier in the chemistry of the unique trichloroacetimidate group and should be amenable to enantioselective developments.[25]

Experimental Section

All experimental details are given in the Supporting Information.

Table 4. Weak BINOL-derived acids in the one-pot BB/BA-catalysed alkylation of hydroxy lactams.



Entry	Substrate	Method[a]	Catalyst	Solvent	Time[b]	Yield
1	**1a**	A	**PA$_I$**	CH_3CN	6 h	74%
2	**1a**	A	**PA$_I$**	CH_2Cl_2	4 h	61%
3	**1a**	A	**PA$_{II}$**	CH_3CN	6 h	59%
4	**1a**	A	**PA$_{III}$**	CH_2Cl_2	12 h	79%
5	**1a**	A	**PA$_{III}$**	CH_3CN	2 h	90%
6	**18**	B[c]	**PA$_I$**	CH_3CN	12 h	0%
7	**18**	B[c]	**PA$_{II}$**	CH_3CN	12 h	12%[d]
8	**18**	B	**PA$_{III}$**	CH_3CN	2 h	100%
9	**18**	B	**PA$_{III}$**	CH_2Cl_2	12 h	0%

[a] *Method A:* 1 mol% DBU and 1.2 equiv Cl_3CCN, room temperature, 30 min, then 1.5 equiv. silyl enol ether and 3 mol% of **PA$_{I-III}$**. *Method B:* 1.5 equiv. silyl enol ether and 2 mol% of **PA$_{I-III}$**.
[b] Unoptimised reaction time referring to the alkylative step.
[c] 5 mol% of the catalyst was used.
[d] Determined by ^{1}H NMR on the crude product.

General Procedure for the Sequential One-Pot BB/BA-Catalysed Intermolecular α-Amidoalkylation of Hydroxy Lactams

To a room temperature solution of hydroxy lactam **1a–h** (0.16 mmol) in 0.5 mL of dichloromethane or acetonitrile (as indicated in the text), trichloroacetonitrile (19 μL, 0.19 mmol, 1.2 equiv.) was added dropwise. After 10 min of stirring, 1 mol% DBU was introduced (6.4 μL). As the transient trichloroacetimidate entities were found to be labile on TLC, readily giving back the starting material, the first step was checked by ^{1}H NMR spectroscopy. Regardless of the nature of both substituent at nitrogen and solvent, the desired trichloroacetimidates were totally formed within 30 min. At this stage, the nucleophile (1.2 equiv. except for allyltrimethylsilane and anisole where 2 equiv. and 4 equiv. are respectively used) and 3 mol% of the acid catalyst (9.6 μL) were added dropwise at room temperature. The end of the reaction was monitored by TLC and the product was purified by flash-column chromatography, eluting with cyclohexane/EtOAc (80/20).

Acknowledgements

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[15] It is worth mentioning that reaction of *N*-phenethyl hydroxy lactam **1f** with allyltrimethylsilane **3e** produced the desired allylated product **2k** quantitatively, with no trace of competitive Friedel–Crafts product[14] being formed (see Supporting Information).

[16] As a representative example, direct reaction of hydroxy lactam **1a** with indole (1.2 equiv.) in the presence of Tf_2NH (2 mol%) was able to provide the corresponding adduct **2h** quantitatively, after 2 h in CH_2Cl_2 at room temperature.

[17] The arylated product **2j** was the major product formed following our procedure. However, this latter could not be isolated from minor side-products by flash chromatography on SiO_2 and yield was estimated from ^1H NMR and GC-MS analyses.

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[24] CH_3CN probably assists the cation formation, as well known in catalytic cationic chemistry.

[25] During the preparation of this manuscript, Fairbanks and co-workers described a chiral phosphoric acid-based catalytic approach to improve the inherent stereoselectivities of glycosylations using trichloroacetimidate sugar donors: D. J. Cox, M. D. Smith, A. J. Fairbanks *Org. Lett.* **2010**, *12*, 1452–1455.

