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Article

Phase-Transfer-Catalyzed Alkylation of Hydantoins

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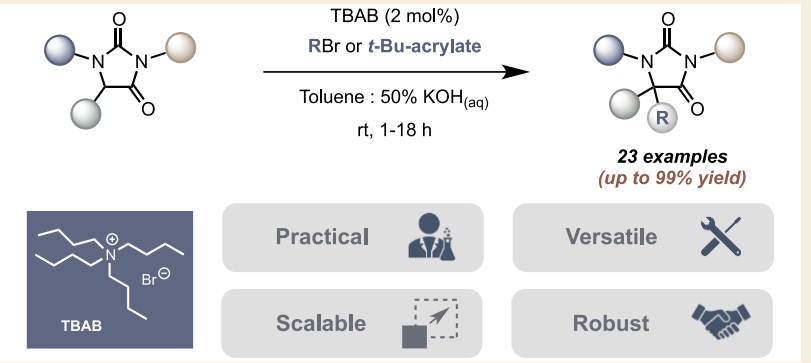

ABSTRACT: A highly efficient, cost-effective, and environmentally friendly protocol is reported for the C5-selective alkylation of hydantoins under phase-transfer catalysis. The reactions are scalable and only require a catalytic amount of tetrabutylammonium bromide (TBAB) to achieve high yields under mild reaction conditions. Moreover, the method is applicable to a wide range of electrophiles, including alkyl-, allyl-, propargyl-, and benzyl halides, as well as acrylates and dibromoalkanes, but also to virtually any hydantoin precursor. We also highlight the potential for an enantioselective adaptation using a chiral phase-transfer catalyst.

KEYWORDS: *phase-transfer catalysis, hydantoins, alkylation, allylation, propargylation, Michael addition*

INTRODUCTION

Imidazolidine-2,4-dione derivatives, commonly referred to as hydantoins, are important scaffolds that exhibit a diverse range of pharmacological and biological properties such as anti-inflammatory, anticonvulsant, anti-HIV, antidiabetic, antimicrobial, and anticancer.[1] With such broad applications, hydantoins are among the most common ring systems in small-molecule marketed drugs.[2] They are also commonly encountered in numerous natural products[3−6] and have found significant synthetic use as versatile reagents,[7] chiral auxiliaries, and directing groups (Figure 1).[8,9] The hydantoin motif is also regularly used as a carboxylic acid bioisostere as well as natural and non-natural amino acid precursors.[10] Given the significance of this particular heterocycle, numerous effective methods have been developed over the years to access this heterocycle, such as the Bucherer−Bergs, Biltz, and Urech syntheses.[11] However, methods that allow a direct and selective C-functionalization of preformed hydantoins are still somewhat scarce.[11−14] Indeed, the current approaches to the desired C-alkylated products typically involve either a two-step protocol featuring aldol condensation followed by reduction/hydrogenation with the possibility of running the reduction in an asymmetric fashion (Figure 2A)[15,16] or direct alkylation that usually requires the use of a strong base (e.g., LiHMDS) and/or cryogenic conditions (Figure 2B).[17] Several examples also involve the highly hazardous combination of NaH and DMF to facilitate alkylation,[18,19] while the use of transition metals in conjunction with strong bases has been reported to catalyze selective C-arylations (Figure 2C).[20] Nonetheless, despite these examples, the direct and selective C-alkylation of hydantoins under mild reaction conditions remains still today an important unaddressed synthetic challenge that we wanted to tackle.

To this end, we envisioned that phase-transfer catalysis using simple, cheap, and readily available catalysts could provide a viable solution (Figure 2D). Indeed, in the 50 years since its discovery, phase-transfer catalysis has become prevalent in practically every area of organic synthesis.[21] Its simplicity, combined with the mild reaction conditions involved, the use of inexpensive and readily available catalysts, and the possibility to easily scale-up the reactions, makes it an invaluable component of the synthetic chemist toolbox all the while holding a solidified position as a sustainable approach. Indeed, considering that the solvent accounts for up to 85% of the mass in the synthesis of an active

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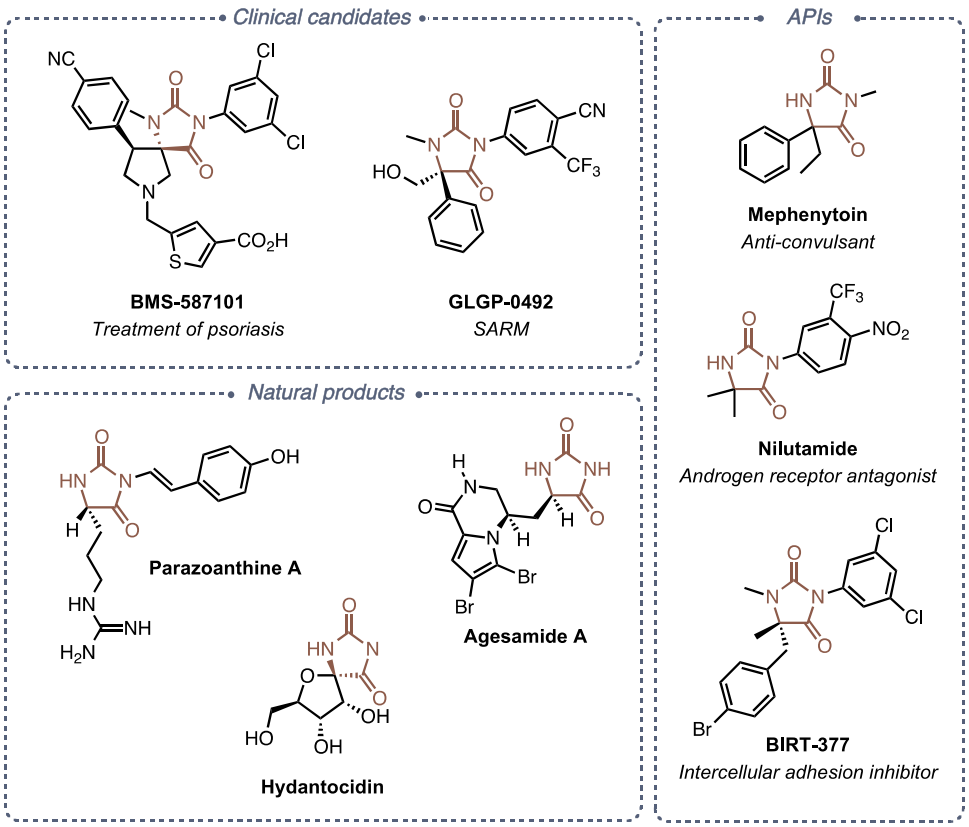

Figure 1. Hydantoin-containing clinical candidates, marketed drugs, and natural products.

pharmaceutical ingredient (API), the replacement of hazardous solvents with more sustainable ones makes the method much more appealing.[22] Another important aspect associated with this methodology is the possibility to run the reaction in an asymmetric fashion using readily available chiral catalysts.[23−27]

RESULTS AND DISCUSSION

To evaluate the feasibility of the method, we chose *N*,*N*-dibenzyl hydantoin **1a** as a model substrate, which was prepared in two steps: one single purification and 75% overall yield starting from commercially available alanine (see the Supporting Information for more details). Given the synthetic utility of the allyl moiety paired with the significance of the hydantoin motif, we decided to initiate this study by evaluating the allylation of **1a** using allyl bromide as the electrophile. Interestingly, the first reaction run using 2 mol % TBAB in a toluene/$KOH_{(aq)}$ mixture afforded the desired allylated product **2a** in a quasi-quantitative yield (96%, Table 1, entry 1). In sharp contrast, the uncatalyzed reaction failed to provide any of the product under otherwise identical conditions (Table 1, entry 2). It is worth pointing out that the use of NaOH instead of KOH slightly reduced the yield (92%, Table 1, entry 1). From here on, we sought to optimize the process from a sustainability standpoint.[28] After consulting several solvent guides,[29,30] we selected CPME, limonene, and anisole as potentially suitable cosolvents. Unfortunately, none of them proved beneficial (Table 1, entries 3−5). Decreasing the concentration of KOH from 50 to 10% w/w resulted in more sluggish reactions (Table 1, entries 6 and 7), while lowering the toluene/$KOH_{(aq)}$ ratio (Table 1, entries 8 and 9) significantly reduced the yield of the reaction potentially due to degradation occurring from the significant increase in base equivalents. Several common phase-transfer catalysts such as tetrabutylammonium iodide (90%), tetrabutylammonium hydrogen sulfate (78%), tetrahexylammonium bromide (86%), and trioctylmethylammonium chloride (74%) were also evaluated but the reactions proved slightly less effective (results are not shown in the table). A final screen to test the catalyst loading found that at 1 and 0.5 mol % (Table 1, entries 10 and 11), the reactions proceeded slowly with incomplete conversion after 24 h. Longer reaction times could obviously improve the conversion; however, as this reduced the practicality of the method, we chose to run all our reactions at 2 mol %.

A series of *N*,*N*-dibenzyl hydantoins derived from phenylalanine (Phe, **1b**, 98%), methionine (Met, **1c**, 97%), phenyl glycine (**1d**, 78%), and glycine (Gly, **1e**, 55%) were efficiently alkylated under the optimized conditions (Figure 3). The latter was isolated and re-engaged to provide bis-allylated product **2f** in 99% yield. The proline-derived hydantoin could also be allylated, albeit with a slightly lower yield (Pro, **1h**, 45%). Interestingly, valine-derived hydantoin **1g** failed to convert under the previous conditions. The use of 58% KOH and 10 mol % TBAB did afford traces of the alkylation product, but the best result (73% yield) was obtained when running the reaction using 50% w/w NaOH and 10 mol % of the catalyst at 40 °C. Considering that the steric hindrance induced by the *i*Pr group can affect multiple factors, we propose two possible scenarios that could potentially account for the observed base effect: (1) the coordination of Na^+ ions provides a lower energy barrier for the deprotonation compared to the corresponding K^+ ions or (2) the Na enolate that is generated undergoes a significantly faster ion exchange with the catalyst. Various substitution patterns on the nitrogen atoms were

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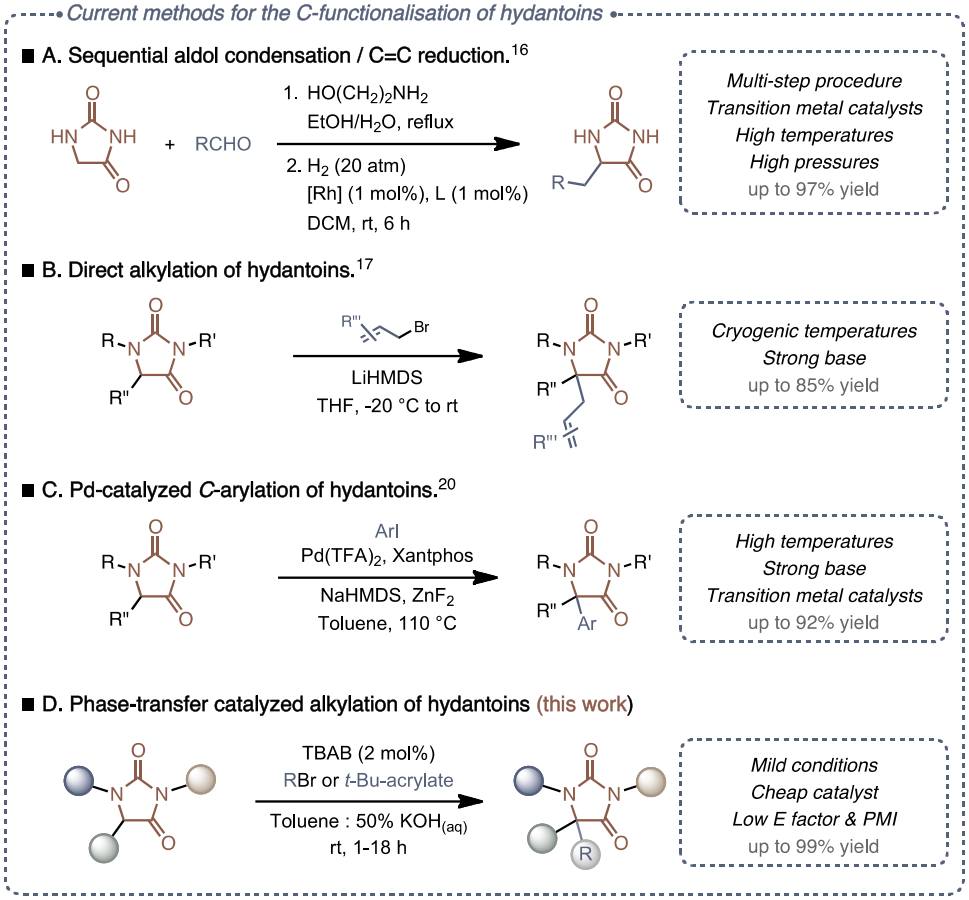
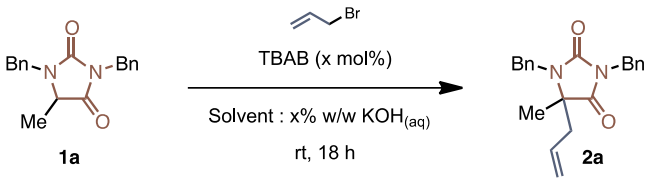


Figure 2. Strategies for the C_5-functionalization of hydantoins.

Table 1. Systematic Study[a]



entry	TBAB (x mol %)	KOH (w/w %)	solvent (org/aq)	yield[b]
1	2	50	toluene (3:2)	96% (92%[c])
2	–	50	toluene (3:2)	traces
3	2	50	CPME (3:2)	52%
4	2	50	limonene (3:2)	73%
5	2	50	anisole (3:2)	68%
6	2	25	toluene (3:2)	19%
7	2	10	toluene (3:2)	6%
8	2	50	toluene (2:3)	66%
9	2	50	toluene (1:4)	62%
10	1	50	toluene (3:2)	37%
11	0.5	50	toluene (3:2)	33%

[a]Reaction conditions: **1a** (0.25 mmol, 1 equiv), allyl bromide (0.75 mmol, 3 equiv), TBAB (x mol %), solvent/$KOH_{(aq)}$ (0.5 mL), rt, 18 h. [b]Isolated yield. [c]Reaction run with 50% w/w NaOH instead of KOH.

eventually tested. *N*-Allyl (**1i**, 86%), *N*-phenyl (**1j**, 84%), *N*-alkyl (**1k**, **1l**, and **1m**, 44−99%), and *N*-PMB (**1n**, 99%) all afforded the corresponding allylated products in high yields.

With these results in hand, we next varied the nature of the electrophile. Interestingly, replacing allyl bromide by prenyl bromide (**1o**, 95%), methallyl bromide (**1p**, 38%), benzyl bromide (**1q**, 73%), propargyl bromide (**1r**, 92%), and bromo *tert*-butyl acetate (**1s**, 77%) proved successful. The use of dibromoalkanes, such as 1,4-dibromo butane, in conjunction with the glycine-derived hydantoin was also effective as showcased by the isolation of the double alkylation spirocyclic product **2t** in 51% yield. Finally, alkylation through a 1,4-addition process using an acrylate as the electrophile also proved feasible, as the corresponding saturated ester **2u** was obtained in a quasi-quantitative yield after only 1 h of reaction. Unfortunately, electrophiles such as benzaldehyde, epibromohydrin, and β-nitrostyrene, which are susceptible to rapid side reactions under highly caustic conditions, did not provide the desired alkylation products. It is worth pointing out that the O-alkylated side products were never observed and can therefore not account for the lower yields that were sometimes obtained. These are either due to poor conversion or ring cleavage, resulting in the unrecovered starting material.

The reaction also proved to be scalable. For example, the allylation of *N*,*N*-dibenzyl hydantoin **1a** run on a 1 g scale afforded the corresponding allylated product **2a** in 96% yield. Similarly, the 1,4-addition run on a 5 g scale afforded alkylated product **2u** in only 1 h and 92% yield after a simple workup and without any further purification (see the Supporting Information for more details). The simplicity of the workup and the isolation procedure led us to study this reaction further. The possibility of recycling the aqueous phase along with the catalyst was first evaluated. Unfortunately, when

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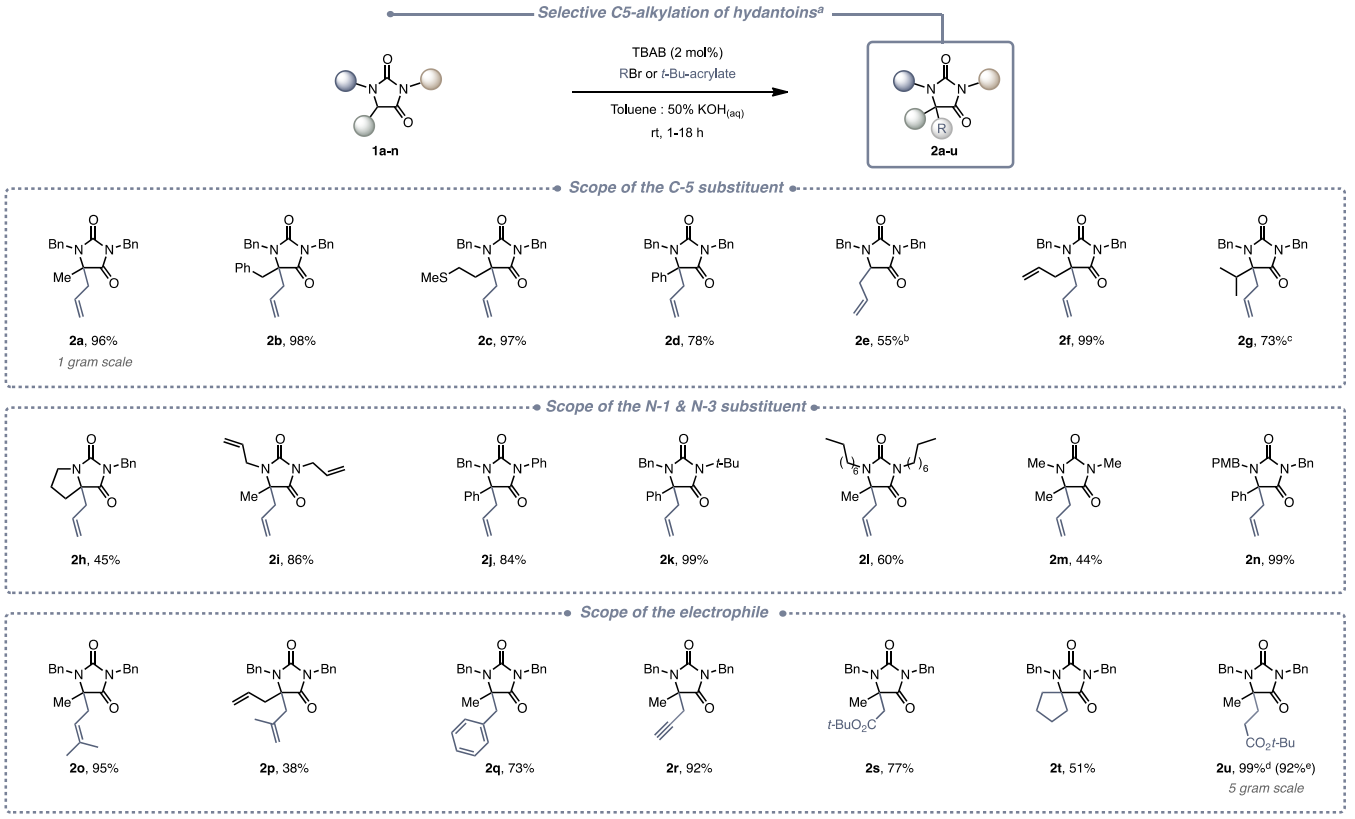

Figure 3. Substrate scope. [a]Conditions: **1a−u** (0.25 mmol, 1 equiv), electrophile (0.75 mmol, 3 equiv), TBAB (0.005 mmol, 2 mol %), toluene (0.3 mL), 50% w/w KOH_{aq} (0.2 mL), rt. [b]1.2 equiv of allyl bromide was used instead of 3. [c]TBAB (0.025 mmol, 10 mol %), 50% w/w $NaOH_{aq}$ (0.2 mL), rt, 48 h. [d]Reaction run with *t*-butyl acrylate. [e]Reaction run on a 5 g scale.

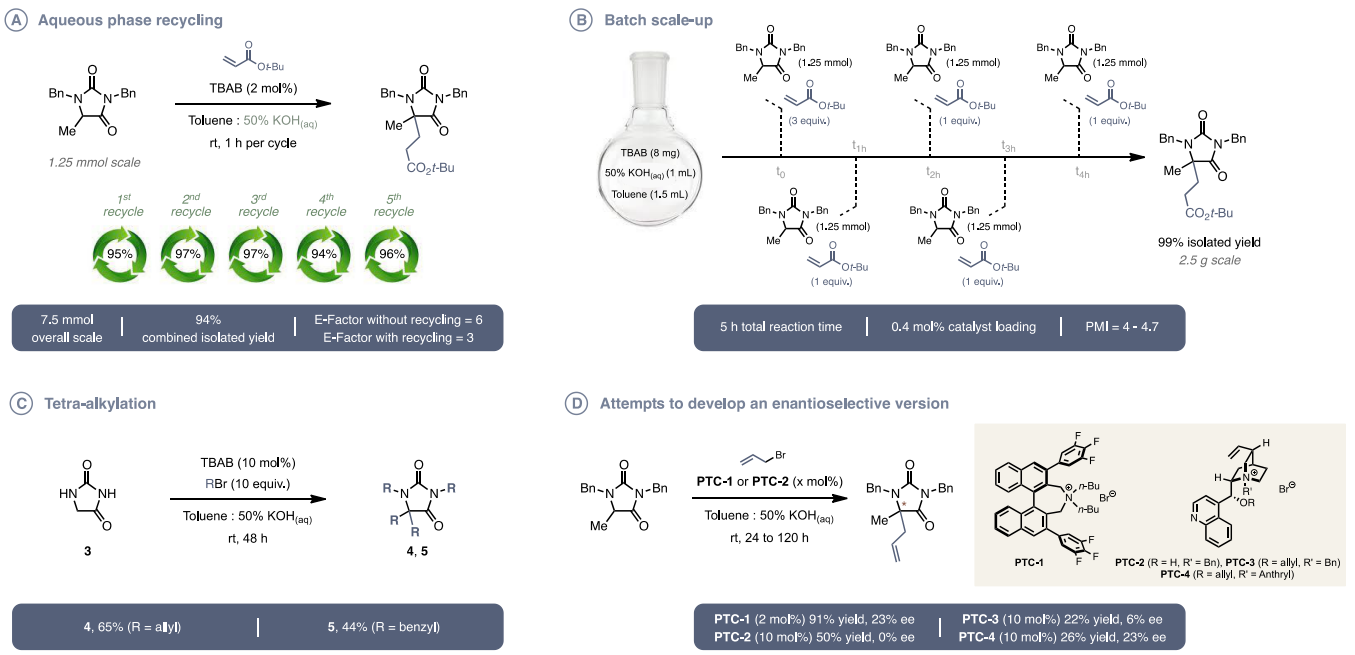

Figure 4. Process optimization, tetra-alkylation and enantioselective studies.

repeating the reaction using the same aqueous phase and without adding any additional phase-transfer catalyst, the reaction stalled. This lack of reactivity could be circumvented by simply adding 2 mol % TBAB before each run. After five runs, the product was filtered through a pad of silica and was washed with hexane to furnish the pure product in 94% combined isolated yield (Figure 4A).

Another scale-up experiment was run using a slightly different protocol. This time, the hydantoin and the acrylate were sequentially added in batches into the same reactor containing one single load of the catalyst and keeping the

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hydantoin/acrylate ratio constant throughout the reaction (Figure 4B). After the fifth run was complete, the slurry was filtered and washed with 5 mL of hexane to recover 86% of the product. Further 13% was recovered from the biphasic filtrate, resulting in a process mass intensity (PMI) of 4−4.7 (see the Supporting Information for calculations). Distillation of the organic phase to recover the excess acrylate as well as toluene and the recycling of the aqueous phase make this process virtually "waste free".

To increase the utility of the method further, we also tested a full alkylation protocol, where both nitrogens and the C5 position are alkylated (Figure 4C). The tetra allylation of the naked hydantoin proceeded smoothly providing **4** in 65% yield. The tetra benzylation also proved successful, although **5** was obtained in a slightly lower yield (44% yield).

After developing a robust alkylation protocol, we sought to develop an asymmetric version of our reaction (Figure 4D). Indeed, to date, there are only a hand full of asymmetric transformations that allow us to control the stereochemistry at the C5 position of a hydantoin; these include the enantioselective hydrogenation catalyzed by chiral rhodium complexes,[16] the diastereoselective aldol using aldehydo sugars,[31] the asymmetric Friedel-Craft alkylation catalyzed by chiral phosphoric acids,[32] and the photochemical deracemization of C5-substituted hydantoins through a reversible hydrogen atom transfer.[33] Besides the aforementioned methods that allow a direct functionalization of hydantoins, there are also several asymmetric syntheses of hydantoins reported in the literature, but they mainly rely on the preinstallation of the chirality prior to the formation of the ring.[34−39] Asymmetric phase-transfer catalysis has become a prominent part of organocatalysis with some fantastic examples reported by Maruoka, Denmark, Itsuno, Kitamura, Park, Andrus, Itoh, Arai, and others.[40,41] For our part, we sought to induce enantioselectivity by replacing TBAB with a chiral phase-transfer catalyst such as **PTC-1**, which was initially developed by Maruoka and co-workers and proved successful in numerous asymmetric alkylation reactions. Unfortunately, the allylation of *N*,*N*-dibenzyl hydantoin **1a** using **PTC-1** afforded the corresponding C5-allylated product **2a** in only 21% ee albeit 91% isolated yield. With this rather disappointing result in hand, we next turned our attention toward the use of cinchona alkaloid-derived catalysts. Unfortunately, the three catalysts tested, **PTC-2**, **PTC-3**, and **PTC-4**, all proved significantly less reactive than **PTC-1**, requiring longer reaction times at higher catalyst loadings. Moreover, none of these catalysts, including the Corey−Lygo catalyst **PTC-4**, which is commonly used in asymmetric phase-transfer catalysis, improved the selectivity previously observed. Nonetheless, these results, while relatively modest, highlight the potential for an enantioselective phase-transfer-catalyzed alkylation of hydantoins, providing sufficient catalyst optimization.

CONCLUSIONS

In summary, we developed an efficient, general, practical, scalable, and potentially waste-free alkylation of hydantoins. Mild reaction conditions coupled with the low cost associated with the use of TBAB and the practicality of the method make it a method of choice for the synthesis of diversely functionalized hydantoins. We also highlighted the potential for an enantioselective adaptation, and work is underway to develop novel catalysts for this asymmetric transformation. Considering the importance of the hydantoin motif in synthetic, medicinal, and agrochemical chemistry, we believe that this method will become an essential tool in the synthetic chemist's toolbox.

EXPERIMENTAL DETAILS

General Alkylation Procedure

To a solution of the hydantoin (0.25 mmol) and TBAB (2 mol %) in toluene (0.3 mL) was added 50% w/w aqueous KOH (0.2 mL), followed by the addition of the respective electrophile (0.75 mmol, 3 equiv) at rt. The reaction was stirred vigorously at the same temperature until complete conversion of the starting material (reaction monitored by TLC), after which the reaction was diluted with H_2O (10 mL) and extracted with DCM (3 × 10 mL). The combined organic phases were then dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to afford a crude residue, which was purified by flash column chromatography over silica gel.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsorginorgau.1c00058.

All experimental details including further optimization studies; detailed procedures; proper characterization of all products; and copies of ^1H and ^{13}C NMR (PDF)

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Author Contributions

All of the authors contributed to and approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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