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On the Chlorenium Source in the Asymmetric Chlorolactonization Reaction

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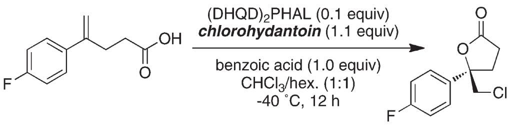
ABSTRACT



N-Acylated N-chlorohydantoins are shown to be competent chlorenium sources in the (DHQD)$_2$PHAL-mediated asymmetric chlorolactonization. The derivatives demonstrate the exact role of the N1 and N3 chlorine atoms in the parent dichlorohydantoins with the N1 chlorine serving as an inductive activator and the N3 chlorine being delivered to the substrate. The putative associated catalyst/chlorine source complex was experimentally demonstrated through a series of matched/mismatched experiments employing chiral N-chlorinated hydantoins.

Recently, a number of new methods for the asymmetric delivery of chiral halenium (X^+) equivalents onto nonchiral olefinic precursors have appeared in the literature.[1] Beginning with Taguchi's carbocyclizations,[2] Kang's cobalt–salen-mediated asymmetric iodoetherification reaction,[3] and Ishihara's iodonium induced polyene cascade cyclization,[4] this traditionally stubborn[5] class of asymmetric transformations has begun to return favorable results in terms of enantioselectivity. Subsequent to these efforts, the Snyder laboratory featured an asymmetric chlorination of an isolated olefin in an advanced intermediate as a key step in the total synthesis of (−)-napyradiomycin A1.[6]

Recently, we discovered a unique catalyst system comprising a catalytic amount of (DHQD)$_2$PHAL and chlorinated hydantoins that allowed for good conversions and enantioselectivities for the chlorolactonization of 4-substituted 4-pentenoic acids (see the transformation in Table 1 for an example).[7] Contemporary with our disclosure, the Tang group reported a highly enantioselective bromolactonization of conjugated (Z)-enynes governed by a cinchonidine-based urea organocatalyst and NBS as a bromine source.[8] Very recently, Veitch and Jacobsen disclosed an aminourea-mediated asymmetric iodolactonization of alkenoic acids that proceeds in high yield and excellent ee's.[9]

In our original disclosure, the use of dichlorohydantoins as the chlorine source proved essential for obtaining the highest possible enantioselectivities. We have subsequently

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(1) (a) For a recent review, see: Chen, G.; Ma, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 8306.

(2) (a) Inoue, T.; Kitagawa, O.; Kurumizawa, S.; Ochiai, O.; Taguchi, T. *Tetrahedron Lett.* **1995**, *36*, 1479. (b) Inoue, T.; Kitagawa, O.; Ochiai, O.; Shiro, M.; Taguchi, T. *Tetrahedron Lett.* **1995**, *36*, 9333. (c) Inoue, T.; Kitagawa, O.; Saito, A.; Taguchi, T. *J. Org. Chem.* **1997**, *62*, 7384. (d) Kitagawa, O.; Taguchi, T. *Synlett* **1999**, 1191.

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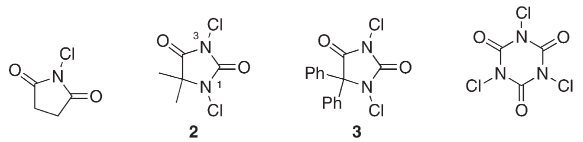
10.1021/ol102850m

set out to explore the mechanism of the transformation with the aim of understanding the drivers responsible for enantioinduction, specifically as they relate to the role of the hydantoin in the reaction. Our initial efforts have focused on exploring the structural and electronic influence of the chlorine source (i.e., **3**).

In this paper, we present a detailed study on the influence of structurally related N1 and N3 acylated *N*-chlorohydantoins on the selectivity of the chlorolactonization reaction. This study was facilitated by the development of a convenient method for the selective synthesis of N1 and N3 acylated hydantoins. Additionally, we provide further evidence for the associative complex between the (DHQD)$_2$-PHAL catalyst and the chlorine source that seems to be influential for the observed selectivity in the transformation.

During our initial optimization studies, it became apparent that dichlorinated hydantoins (i.e., **3**) were suited as a perfectly tuned halenium source for our methodology. The reagent appeared uniquely wedged in reactivity between *N*-bromosuccinimide, which resulted in a fast but less selective bromolactonization, and *N*-chlorosuccinimide, which was slow to react at low temperatures in the analogous chlorolactonization (Table 1, **1**, vide infra). The ^{35}Cl nuclear quadrupole resonance (NQR) frequency has been invoked as a quantitative marker for the relative Cl$^+$ character of a given N−Cl bond. In particular, a larger Cl$^+$ character corresponds to a higher NQR resonance frequency.[10] Several resonance frequencies are collected in Figure 1.



1
54.095 MHz

2
N1: 53.648 MHz
N3: 55.962 MHz

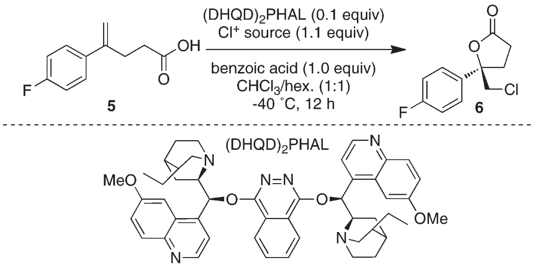
3
N1: 55.019 MHz
N3: 56.460 MHz

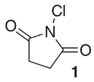
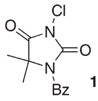
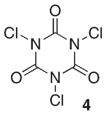
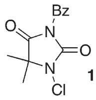
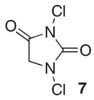
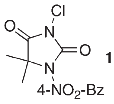
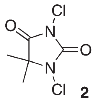
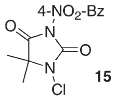
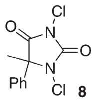
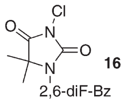
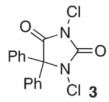
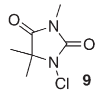
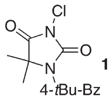
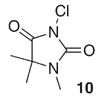
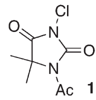
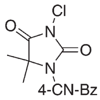
4
58.902 MHz

Figure 1. Selected NQR resonance frequencies.

On the basis of the NQR resonance frequencies collected in Figure 1, one would expect that the N3 chlorines (see **2** for numbering) of hydantoins **2** and **3** would be more electrophilic than that of NCS (**1**), while the N1 chlorine atoms should possess roughly the same level of electrophilicity as **1**. Additionally, one would expect TCCA (**4**)[11] to possess even more electrophilic Cl atoms than the *N*-chlorohydantoins and NCS.

Table 1. Cyclization with Modified *N*-Chlorohydantoins



entry	Cl$^+$ source	% yield^a	% ee^b	entry	Cl$^+$ source	% yield^a	% ee^b
1	 **1**	15	52	10	 **12**	78	88
2	 **4**	89	70	11	 **13**	21	43
3	 **7**	76	81	12	 **14**	71	86
4	 **2**	87	84	13	 **15**	14	46
5	 **8**	82	85	14	 **16**	64	87
6	 **3**	81	89	15	 **17**	86	88
7	 **9**	7	72	16	 **18**	64	87
8	 **10**	50	78	17	 **19**	67	88
9	 **11**	71	83	18	 **20**	78	84

^{a} Yields are isolated yields after column. ^{b} As judged by chiral GC.

This general trend, as predicted by the NQR resonance frequencies, is evident in the chlorolactonization of *p*-fluorophenyl-substituted alkenoic acid **5** to give chlorolactone **6** (Table 1). Under our optimized conditions, the cyclization of **5** governed by NCS (entry 1) proceeds in a relatively poor (15%) yield with a reduced enantioselectivity of just 52% ee. A series of dichlorinated hydantoins (entries 3−6) produced the desired chlorolactone **6** in a much higher yield (76−87%) and markedly improved ee's (81−89% ee) as compared to **1**.[12] Chlorolactonization

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(12) For comparison with NCS (**1**), *N*-chlorophthalamide and 4-nitro-*N*-chlorophthalamide were used in the standard reaction depicted in Table 1, leading to 4% (13% ee) and 7% (32% ee) of **6** in 12 h, respectively.

with the more electrophilic TCCA (**4**, entry 2) returned chlorolactone **6** in the highest yield (89%), but with a reduced 70% ee as compared to the *N*-chlorohydantoin series. The lower enantioselectivity with the more reactive TCCA may be due to an inherently nonselective uncatalyzed background reaction (see the Supporting Information) that is avoided with the less reactive chlorohydantoins.

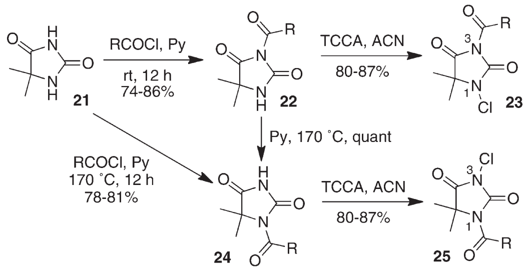
This trend indicates that the N3 chlorine of hydantoin **3** is delivered to the substrate in the chlorolactonization reaction, since the N1 chlorine atom is substantially less electrophilic (i.e., on the order of **1**, see Figure 1). Indeed, we were able to observe the immediate formation of the 1-chloro-3-hydro hydantoin byproduct by ^{1}H NMR during the course of the reaction.[7] The N1 chlorine of **3** must then chiefly serve to inductively activate the N3 chlorine atom and likely accounts for the molecule's enhanced N3 NQR resonance frequency as compared to NCS. A substantial amount of evidence for this supposition was collected by screening a series of *N*-chlorinated hydantoins.

The 1-chloro-N3-methyl-5,5-dimethylhydantoin (**9**, entry 7) was virtually inactive in the conversion of **5**, returning just 7% yield of **6** in 72% ee. This outcome was not unexpected, given that the remaining N1 chlorine of **9** is flanked by just one carbonyl and thus ought to be even less active than NCS (cf. entry 1). More interestingly, when the inductively activating N1 chlorine was replaced by a methyl (**10**, entry 8), the remaining N3 chlorine was substantially less activated, returning **6** in a reduced yield of 50% and with reduced selectivity of 78% ee. Clearly, some modicum of inductive activation at the N3 position via substitution at the N1 position is desirable in terms of both enhanced yield and enantioselectivity.

We posited that one might be able to rescue both yield and enantioselectivity in the transformation if the N1 chlorine of the chlorenium source were replaced by another activating group. Additionally, by incorporating a series of substitutions at the N1 site, we would be able to probe any steric demands that might arise in the associative complex between catalyst and hydantoin.[7]

After some experimentation, we arrived at a simple method for the selective acylation of the N1 and N3 positions of 5,5-dimethylhydantoin **21** (Scheme 1). The N3 position (i.e., **22**) could be selectively acylated under mild conditions by treating **21** with the appropriate acyl chloride in pyridine at room temperature. Alternatively, heating a pyridine solution of **21** and the acyl chloride to 170 °C gave selective access to the N1 acylated product **24**. Suspecting the intermediacy of **22** in the latter transformation, we also demonstrated its quantitative conversion to **24** on heating in pyridine at 170 °C. The *N*-acyl hydantoins were then converted to their corresponding monochlorinated derivatives **23** and **25** in good yield (80−87%) by employing our TCCA mediated chlorination protocol.[13] Thus, N1 and N3 acyl and benzoyl hydantoins **11**−**20** were generated, and the position of acylation and subsequent chlorination was secured unequivocally by X-ray crystallography (see the Supporting Information for details).

Scheme 1. Preparation of *N*-Aacyl-*N*-chlorohydantions



With **11**−**20** in hand, they were next screened as chlorenium sources in the chlorolactonization of **5**, providing chlorolactone **6**. Confirming our prediction, all eight of the N1 acylated chlorine sources returned the desired lactone **6** in comparable yields and good enantioselectivities (on average 72% yield, 86% ee). The N1 acetylated hydantoin **11** gave **6** in 71% yield and 83% ee (entry 9). Interestingly, **11** was nearly equally selective as the parent 1,3-dichloro-5,5-dimethylhydantoin **2** and markedly more active and selective than the N1 methyl derivative **10**. The N1 benzoyl derivative **12** surpasses the parent hydantoin **2** in terms of selectivity, returning **6** in 88% ee with a slightly reduced yield of 78% (entry 10). Conversely, the N3 benzoyl congener (**13**) produced **6** in substantially lower yield and reduced enantioselectivity (21% yield, 43% ee, entry 11). A second example of an N3 *p*-nitrobenzoyl-substituted chlorohydantoin also performed poorly in the conversion of **5** to **6** (14% yield, 46% ee, entry 13). The latter two examples clearly point to the need for an electron-withdrawing group on N1 for the activation and reactivity of the N3 chlorine.

Next, we screened a series of N3-chlorinated hydantoins containing a variety of substituted benzoyl groups at the N1 position (**14**, **16**−**20**). Interestingly, all of the compounds returned **6** with good ee's ranging from 84 to 88% ee (entries 12, 14−18).

To more closely probe the magnitude of the electronic effects of the N1 benzoyl substituent, we measured the rate of the formation of lactone **6** by NMR studies (see the Supporting Information for details). We employed hydantoins **12**, **14**, **16**, **17**, **19**, and **20** in order to scan a range of electron-donating and -withdrawing substituents. Interestingly, we observed a clear rate acceleration when hydantoins harboring electron-withdrawing *N*-benzoyl substituents

Table 2. Calculated Rate Constants for the Formation of the Lactone **6** by Using Different N1 Benzoylated Hydantoins (1 mol % Catalyst)

hydantoin	k (s^{-1})	hydantoin	k (s^{-1})
17	1.6×10^{-4}	**16**	4.2×10^{-4}
12	2.1×10^{-4}	**20**	5.6×10^{-4}
19	2.4×10^{-4}	**14**	7.4×10^{-4}

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(13) Whitehead, D. C.; Staples, R. J.; Borhan, B. *Tetrahedron Lett.* **2009**, *50*, 656.

were employed (Table 2). For example, by removing the methyl group from the benzoyl group the rate constant increases from 1.6×10^{-4} to 2.1×10^{-4} (cf. **17** vs **12**). By adding another fluoro group to the ortho postion of the hydantoin **19** the rate constant was almost doubled (4.2×10^{-4} vs 2.4×10^{-4}; **16** vs **19**). Moreover, the rate acceleration was even more pronounced when more strongly electron-withdrawing substituents were employed (i.e., 5.6×10^{-4} and 7.4×10^{-4} for **20** and **14**, respectively).

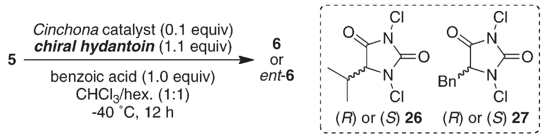
That the reaction maintains a comparable degree of selectivity regardless of the substitution on the N1 benzoyl substituent illustrates two interesting points. First, the overall electronics of the benzoyl substituent does not seem to influence the enantioselectivity of the transformation to any appreciable extent aside from behaving as a surrogate activating group in place of the N1 chlorine in DCDMH (**2**) and DCDPH (**3**). Sadly, this frustrates any strategy toward further optimization of the enantioselectivity of the transformation by means of electronic fine-tuning of the N1 benzoyl substituent, although the electronic effects of the substituted benzoyl group do translate to the reactivity of the distal N3 chlorine to some extent as shown by the rate data in Table 2.

Second, the steric demand of the substituents on the N1 benzoyl moiety seems to have a negligible effect on the selectivity of the transformation. It seems logical that since the active N3 chlorine is distal to the benzoyl group at N1, one would not expect the steric bias at the N1 position to influence the approach of the alkenoic acid to the pre-organized catalyst/chlorine source complex. More interesting is the implications of the N1 substitutent on the catalyst/hydantoin complex itself. Apparently, the N1 nitrogen and its substituent, regardless of size, must be splayed in a manner such that it does not clash with the chiral catalyst, thus allowing for high enantioselectivity. This fact, taken together with the clear dependence of ee on the size of the C-5 substituents (see entries 3−6), may suggest that the complex between the catalyst and the hydantoin is governed by a hydrogen bond to the C-4 carbonyl in lieu of that housed in the C-2 position.

In addition to screening the series of *N*-acyl hydantoins, we also wished to probe the associative hydantoin/catalyst complex observed previously by ^{1}H NMR spectroscopy.[7] We surmised that an appropriate means of experimentally demonstrating the formation of the hydantoin/catalyst complex might be to employ a series of enantiomerically pure *N*-chlorinated hydantoins in the presence of the chiral catalyst in the conversion of **5** to **6**. If the enantiomerically pure hydantoins engaged in an associative interaction with the $(DHQD)_2PHAL$ catalyst, then the stereochemical antipodes of the chlorine source ought to reflect matched/mismatched behavior in terms of enantioselectivity in the preparation of **6**. For this study, we prepared both enantiomers of 5-isopropyl (**26**) and 5-benzyl-1,3-dichlorohydantoin (**27**). We have already demonstrated the ability to chlorinate chiral hydantoins without eroding their enantiopurity.[13]

When the *R* and *S* enantiomers of **26** were employed in the cyclization of **5** with $(DHQD)_2PHAL$ under optimized conditions, clear matched/mismatched behavior was observed (Table 2). In the presence of (*S*)-**26**, lactone **6** was returned in 78% yield and 83% ee, while the *R* antipode gave **6** in a substantially reduced yield of 44% with an eroded enantioselectivity of 69% ee. This result again clearly demonstrates the formation of an associative complex between the chiral catalyst and the chlorine sources. The reduced yield for the mismatched case (i.e., with (*R*)-**26**) might indicate that the C-5 substituent is displayed in the transition state in such a manner so as to prevent facile approach of the substrate to the catalyst/hydantoin complex. Importantly, the opposite effect was observed when the pseudoenantiomer $(DHQ)_2PHAL$ was employed as the chiral catalyst, albeit to a lesser extent. In that case, the *R* enantiomer of **26** returned lactone *ent*-**6** in higher yield and ee (65% yield, 62% ee) as compared to the *S* antipode (30% yield, 55% ee). The overall lower selectivity when $(DHQ)_2PHAL$ is employed is likely due to its diastereomeric relationship with its more selective pseudoenantiomer $(DHQD)_2PHAL$. A similar but less pronounced effect was observed with (*S*)- and (*R*)-**27** (Table 3, entries 3 and 4), possibly as a result of benzyl's smaller steric demand as compared *iso*-propyl.

Table 3. Matched/Mismatched Behavior with Chiral *N*-Chlorohydantoins



N-chlorohydantoin		$(DHQD)_2PHAL$		$(DHQ)_2PHAL$	
entry		% yield of **6**	% ee of **6**	% yield of *ent*-**6**	% ee of *ent*-**6**
1	(*S*)-**26**	78	83	30	−55
2	(*R*)-**26**	44	69	65	−62
3	(*S*)-**27**	78	79	71	−71
4	(*R*)-**27**	71	75	71	−73

In summary, we have probed the nature of the chlorenium source in our asymmetric chlorolactonization protocol by preparing a series of previously unknown *N*-acylated *N*-chlorohydantoins. We have conclusively secured the role of the N1 chlorine as an inductive activator of the N3 chlorine, which in turn is delivered to the substrate during the course of the chlorolactonization event. Finally, we experimentally demonstrated the formation of the previously observed associative complex between the chiral catalyst and chlorohydantoin by performing the chlorolactonization in the presence of chiral *N*-chlorohydantoins.

Acknowledgment. We acknowledge the ACS PRF (No. 47272-AC) and the NSF (CHE-0957462) for funding.

Supporting Information Available. Experimental details for synthesis of hydantoins along with X-ray crystal structure of select compounds. This material is available free of charge via the Internet at http://pubs.acs.org.