Chemical Science

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Cite this: *Chem. Sci.*, 2016, 7, 1057

Chiral Brønsted acid-catalyzed enantioselective Friedel–Crafts reaction of 2-methoxyfuran with aliphatic ketimines generated *in situ*†

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Received 26th August 2015
Accepted 29th October 2015

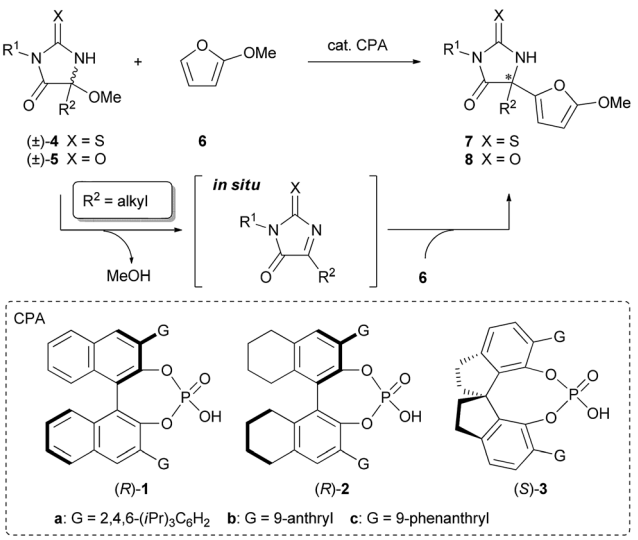
DOI: 10.1039/c5sc03175c

www.rsc.org/chemicalscience

An enantioselective Friedel–Crafts reaction with aliphatic ketimines generated *in situ* from hemiaminal ethers catalyzed by a chiral Brønsted acid was investigated. The reaction of 2-methoxyfuran with (thio) hydantoin-derived hemiaminal methyl ether proceeded under the influence of a chiral phosphoric acid catalyst to afford the corresponding adduct possessing a quaternary stereogenic center in high yield with high enantioselectivity. Theoretical studies were also conducted to clarify the mechanism of the stereochemical outcome and the major factors contributing to the efficient enantioselection.

The Friedel–Crafts reaction is one of the most important carbon–carbon bond-forming reactions in organic chemistry. In recent years, the enantioselective Friedel–Crafts reaction using organocatalysis has emerged as a powerful method for the synthesis of enantio-enriched compounds.[1] In particular, reactions employing unsymmetrical ketimines as electrophiles have received much attention because of the utility of the adducts, chiral amines possessing a quaternary stereogenic center. Although a number of reactions have been developed to date,[2] limitations remain on the applicability for ketimines and nucleophiles. For instance, the reactions employing aliphatic ketimines have largely been unexploited. Hence the development of reactions applicable to a range of ketimines substituted by alkyl groups is still a challenging topic.[3] In addition, indoles and pyrroles are the only nucleophiles that have achieved a high enantioselectivity so far. In this context, we envisaged to develop a new enantioselective Friedel–Crafts reaction of aliphatic ketimines that have a variety of alkyl substituents with the expanding scope of nucleophiles using chiral phosphoric acid (CPA) as a chiral Brønsted acid catalyst.[4] From a mechanistic viewpoint of the chiral phosphoric acid-catalyzed reaction, the origin of the stereochemical outcome in the carbon–carbon (C–C) bond-forming reaction of the aliphatic ketimine has scarcely been investigated[5] despite conducting detailed studies of the enantioselective reduction of ketimines.[6] To establish the enantioselective Friedel–Crafts reaction of aliphatic ketimines followed by the acquisition of mechanistic insight into the stereo-determining step, we designed the reaction system shown in Scheme 1.

For the development of the reaction employing aliphatic ketimines as a substrate, one often encounters a problem based not only on poor reactivity of aliphatic ketimines but also on their stability and synthetic difficulty. Thus we envisioned utilizing thiohydantoin derivatives **4** and hydantoin derivatives **5**, which possess a hemiaminal ether moiety, as precursors for the aliphatic ketimines. With these substrates, the corresponding ketimines are generated *in situ* through the



Scheme 1 Reaction design.

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† Electronic supplementary information (ESI) available: Experimental procedures, exploratory investigation of the reaction conditions, characterization data and DFT studies. CCDC 1405286. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5sc03175c

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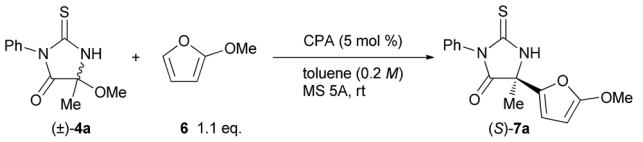
elimination of alcohols under the influence of a Brønsted acid catalyst,[7] and an imine carbon is activated by an electron-withdrawing group and there is a sterically less congested environment around the imine carbon because of their planarity. The utilization of (thio)hydantoin derivatives as substrates is also attractive from the synthetic point of view. The products of the designed reaction are (thio)hydantoin derivatives that have a quaternary stereogenic center at the 5-position, these are known as an important class of biologically active molecules with broad medicinal and agrochemical applications,[8–11] and can act as precursors of α-amino acid derivatives by hydrolysis. Furthermore, 2-methoxyfuran (**6**) was chosen as a reactant to expand the scope of nucleophiles, of which the product subunit can potentially function as a handle for further manipulation of the products.[12] Herein we report the enantioselective Friedel–Crafts reaction of 2-methoxyfuran with aliphatic ketimines generated *in situ* catalyzed by chiral phosphoric acid to provide (thio)hydantoin derivatives containing a quaternary stereogenic center in a highly stereoselective manner. Theoretical studies were also conducted to clarify the mechanism of the stereochemical outcome and the major factors contributing to the efficient enantioselection.

The initial experiment was performed with racemic hemiaminal methyl ether **4a**, having a methyl group as a substituent on the imine carbon, and 2-methoxyfuran (**6**) in the presence of a catalytic amount of chiral BINOL-derived phosphoric acid (*R*)-**1a** in toluene (Table 1, entry 1). Pleasingly, the reaction proceeded smoothly in the presence of molecular sieves (MS) 5A which were employed to scavenge methanol generated during the formation of the ketimine. The desired product **7a** was obtained at a high yield albeit with moderate enantioselectivity. Evaluation of several phosphoric acids including chiral BINOL-derived (*R*)-**1** having different substituents at the 3 and 3′-positions, chiral H_8-BINOL-derived (*R*)-**2**, and chiral SPINOL-derived (*S*)-**3**, revealed that (*S*)-**3c** was the optimal phosphoric acid and resulted in a 94% yield with 92% ee (entry 7). Further improvement in both yield and ee value was achieved by using benzene as the solvent instead of toluene (entry 8).[13]

In order to clarify the origin of the stereochemical outcome, we then conducted theoretical studies of the transition states of the stereo-determining C–C bond-forming step. Four transition structures of the C–C bond-forming step were possible through the combination of the *re*- and *si*-faces of the pro-chiral reactants, the ketimine and 2-methoxyfuran (**6**) (Fig. 1). In the transition states **TSss** affording (*S*)-**7a**, the *si*-face of the ketimine reacts with the *re*- and *si*-faces of 2-methoxyfuran (**6**), generating **TSs-*re*** and **TSs-*si***, respectively. Similarly, **TSr-*si*** and **TSr-*re*** were generated for **TSr**s, which results in the formation of (*R*)-**7a**. The geometries of the **TSs**s and **TSr**s were fully optimized and characterized using frequency calculations at the B3LYP level of density functional theory with the 6-31G* basis set.[15,16] After thorough screening of plausible transition structures to determine the relative location of the reactants and the chiral phosphoric acid catalyst, four transition structures of the corresponding configurations were localized. In each optimized structure, the ketimine and 2-methoxyfuran (**6**) interact with the catalyst through an O···H···N hydrogen bond and a C–H···O hydrogen bond, respectively.[17] The **TSs-*si*** and **TSr-*re*** were energetically less favorable than the **TSs-*re*** and **TSr-*si***, presumably due to the steric repulsion between the *N*-phenyl substituent of the ketimine and the methoxy group of **6** (dashed curves in Fig. 1). More importantly, the transition state **TSs-*re*** [which affords (*S*)-**7a**] was more stable than the **TSr-*si*** [which

Table 1 Screening of reaction conditions[a]



Entry	CPA	Time (h)	Yield[b] (%)	ee[c] (%)
1	(*R*)-**1a**	4	92	57
2	(*R*)-**1b**	6	84	84
3	(*R*)-**1c**	4	68	75
4	(*R*)-**2b**	4	76	76
5	(*R*)-**2c**	6	68	70
6	(*S*)-**3b**	4	86	68
7	(*S*)-**3c**	4	94	92
8[d]	(*S*)-**3c**	4	>99	93

[a] Reaction conditions: **4a** (0.10 mmol), **6** (0.11 mmol), CPA (5.0 μmol), MS 5A (100 mg), toluene (0.50 mL). [b] Isolated yields. [c] Enantiomeric excess of **7a** was determined by chiral stationary phase HPLC analysis. Absolute configuration of **7a** was determined to be *S* by X-ray crystallographic analysis.[14] See the ESI for detail. [d] Benzene was used as a solvent instead of toluene.

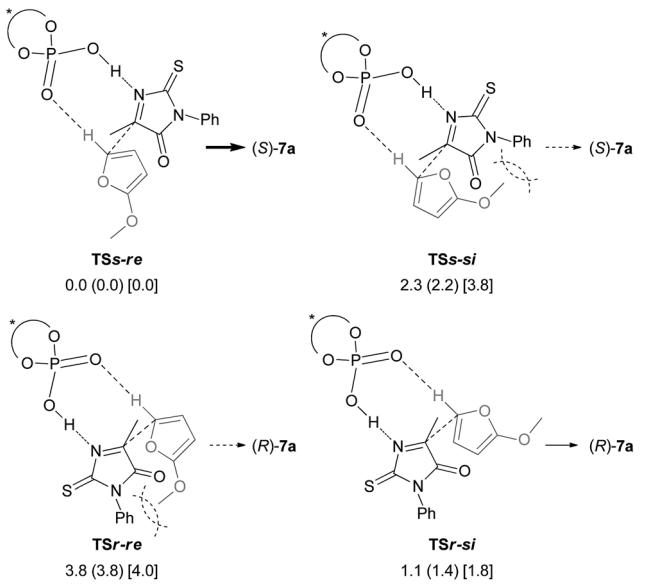


Fig. 1 Schematic representation models of TSss and TSrs. The relative energies of the optimized structures in the gas phase are shown in kcal mol^{-1}, with relative Gibbs free energies (kcal mol^{-1}) in parentheses. The relative energies (kcal mol^{-1}) which were obtained by single-point energy calculations at the B3LYP/6-311+G** level using the SCRF method based on PCM (ϵ = 2.2706 for benzene) are shown in brackets.[18] Steric repulsions are indicated by dashed curves.

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affords (*R*)-**7a**]. The (*S*)-selective pathway was energetically favorable for the reaction catalyzed by (*S*)-**3c**, which is consistent with the experimental results.

Further structural analyses of **TS*s-re*** and **TS*r-si*** allowed the identification of the major factors contributing to the efficient enantioselection. Three-dimensional transition structures of **TS*s-re*** and **TS*r-si*** are illustrated in Fig. 2. As pointed out in Fig. 1, the hydrogen atom at the 5-position of 2-methoxyfuran (**6**) interacts with chiral phosphoric acid (*S*)-**3c** through the C–H···O hydrogen bond (dashed blue lines in Fig. 2). In fact, the distances between the hydrogen and oxygen atoms (1.99 Å in **TS*s-re*** and 2.05 Å in **TS*r-si***) are significantly shorter than the sum of the van der Waals radii of the hydrogen and oxygen atoms (*ca.* 2.7 Å). Furthermore, the ketimine is activated *via* protonation by chiral phosphoric acid (*S*)-**3c** to form the O···H···N hydrogen bond (dashed blue lines in Fig. 2). More interestingly, in both of the transition states, an additional C–H···O hydrogen bond forms between the α-hydrogen atom of the methyl group attached to the ketimine and the phosphoryl oxygen of (*S*)-**3c** (2.25 Å in **TS*s-re*** and 2.14 Å in **TS*r-si***) (dashed red lines in Fig. 2). It can be considered that these two hydrogen bonds, O···H···N and C–H···O, fix the relative location between the ketimine and chiral phosphoric acid (*S*)-**3c**. It is obvious that the observed high enantioselectivity stems from the formation of the hydrogen bond network among the triad of components, resulting in a conformational fixation of the transition states. In the energetically favorable **TS*s-re***, the ketimine and **6** are nearly parallel to the phenanthryl plane of the catalyst substituent to avoid steric congestion (Fig. 2a). In contrast, in the less-favorable **TS*r-si***, both the ketimine and **6** are inserted perpendicularly between two phenanthryl planes (Fig. 2b), in which the methyl group of the ketimine locates close to the bottom phenanthryl substituent. This unfavorable interaction results in steric repulsion between the reactant and the catalyst (Fig. 2b), which would destabilize **TS*r-si***.

The scope of the thiohydantoin derivatives were further investigated under the optimized reaction conditions (Table 2, entries 1–12). Initially, different alkyl substituents at the 5-position were examined (entries 1–4). The reaction of isobutyl-substituted **4b** proceeded smoothly to provide **7b** in a high yield with a high ee (entry 1).[19] In contrast, benzyl-substituted **4c** required a longer reaction time for the full conversion of the substrate, and **7c** was obtained in a moderate yield with a moderate enantioselectivity (entry 2). On the basis of the

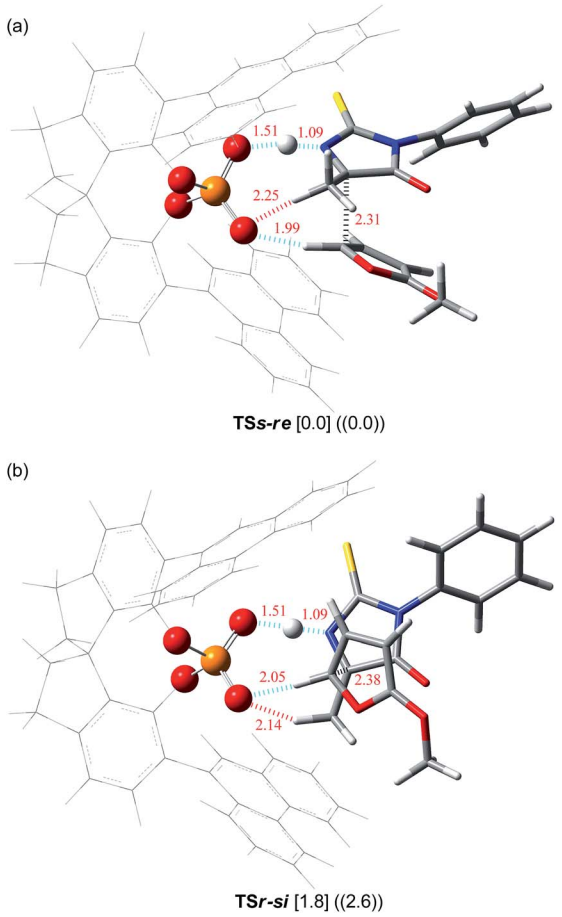
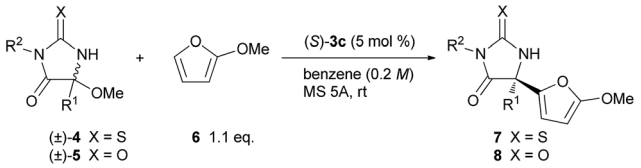


Fig. 2 Three-dimensional structures of transition states (a) TS*s-re* and (b) TS*r-si*. Relative energies (in kcal mol^{-1}) obtained by single-point energy calculations at the B3LYP/6-311+G** level and the M06-2X/6-311+G** level with the SCRF method based on PCM (ϵ = 2.2706 for benzene) are shown in brackets and double parentheses, respectively.[18] Bond lengths are shown in red (Å).

Table 2 Substrate scope[a]



Entry	4 or 5	R^1	R^2	7 or 8	Time (h)	Yield[b] (%)	ee[c] (%)
1	**4b**	*i*Bu	Ph	**7b**	4	98	86
2	**4c**	Bn	Ph	**7c**	48	67	65
3	**4d**	*i*Pr	Ph	**7d**	48	50[d]	85
4[e]	**4d**	*i*Pr	Ph	**7d**	24	89	78
5[f]	**4e**	Me	4-$MeOC_6H_4$	**7e**	4	87	90
6	**4f**	*i*Bu	4-$MeOC_6H_4$	**7f**	4	98	90
7	**4g**	Me	4-BrC_6H_4	**7g**	4	97	90
8	**4h**	*i*Bu	4-BrC_6H_4	**7h**	4	99	88
9	**4i**	Me	3-BrC_6H_4	**7i**	4	99	88
10	**4j**	Me	2-BrC_6H_4	**7j**	6	86 (dr = 3 : 2)	67/94
11	**4k**	Me	Bn	**7k**	4	98	90
12	**4l**	*i*Bu	Bn	**7l**	4	99	90
13	**5a**	Me	Ph	**8a**	24	86	93
14	**5b**	*i*Bu	Ph	**8b**	24	98	92
15[g]	**5c**	*i*Pr	Ph	**8c**	48	51	89
16	**5d**	Me	Bn	**8d**	36	95	93
17	**5e**	*i*Bu	Bn	**8e**	36	97	92

[a] Reaction conditions: **4** or **5** (0.10 mmol), **6** (0.11 mmol), (*S*)-**3c** (5.0 μmol), MS 5A (100 mg), benzene (0.50 mL). [b] Isolated yields. [c] Enantiomeric excess of **7** and **8** were determined by chiral stationary phase HPLC analysis. [d] 35% of **4d** was recovered with 99% ee. [e] Reaction was performed at 50 °C. [f] 1.0 mL of benzene was used. [g] 10 μmol of (*S*)-**3c** (10 mol%) was used.

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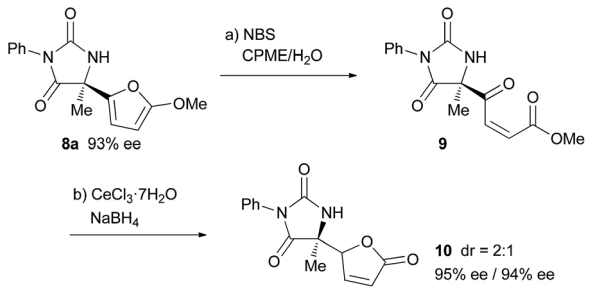
favorable transition state **TS*s-re*** as shown in Fig. 2a, the observed stereochemical outcome presumably arises from the steric repulsion between the phenanthryl substituent of catalyst **3c** and the benzyl moiety introduced to substrate **4c**. In this case, a substantial amount of enamide was formed *via* tautomerization of the imine generated *in situ*. The isopropyl-substituted **4d** also could be applied to this reaction to yield **7d** with high enantioselectivity;[19] however, the reaction at room temperature did not achieve full conversion of the substrate, even after 24 h, and a considerable amount of **4d** was recovered (entry 3). The ee of the recovered **4d** showed that it was enantiomerically pure, indicating that kinetic resolution of **4d** occurred during the elimination of methanol to generate ketimine under the influence of the chiral phosphoric acid catalyst.[20] The higher temperature accelerated the reaction, however the ee was reduced (entry 4). Next, the effect of a substituent on the nitrogen at the 3-position was investigated. Substrates having an electron-donating group as well as an electron-withdrawing group at the *para* position of the phenyl group underwent a reaction to provide the corresponding products in high yields with high enantioselectivities (entries 5–8). *meta*-Bromophenyl-substituted **4i** was also applicable to the reaction without any problem (entry 9). The reaction with *ortho*-bromo-substituted **4j** provided a mixture of diastereomers due to the central chirality at the 5-position and the axial chirality around the C–N bond between the *ortho*-bromophenyl group and the nitrogen at the 3-position (entry 10). The ee of the major diastereomer was moderate while that of the minor diastereomer was very high. The benzyl group was also a suitable substituent on the nitrogen, and the corresponding product was obtained in a high yield with a high ee (entries 11 and 12). The scope of this reaction was expanded by using the hydantoin derivatives **5** in addition to the thiohydantoin derivatives **4** (entries 13–17). Although the reaction of **5** required a longer reaction time compared with that of **4**, the corresponding products **8** were obtained in high yields with high enantioselectivities, except for **8c** which has an isopropyl group (entry 15).

Finally, derivatization of the product based on the 2-methoxyfuryl moiety was performed (Scheme 2). The cleavage of the furan ring of **8a** proceeded smoothly under Achmatowicz type reaction conditions,[21] and subsequent chemoselective reduction of the keto moiety under Luche conditions resulted in the formation of butenolide **10** in a good yield over two steps. In the course of the derivatization, the loss of enantiomeric purity did not occur.[22]



Scheme 2 Derivatization of **8a**. Reagents and conditions: (a) NBS (1.1 eq.), CPME/H_2O, 0 °C, 30 min. (b) $CeCl_3 \cdot 7H_2O$ (1.5 eq.), $NaBH_4$ (1.0 eq.), −78 °C to rt, 3 h, 78% (over 2 steps), dr = 2 : 1, 95% ee/94% ee.

Conclusions

In conclusion, we have successfully developed an enantioselective Friedel–Crafts reaction of 2-methoxyfuran with aliphatic ketimines generated *in situ* from thiohydantoin- and hydantoin-derived hemiaminal methyl ether under the influence of a chiral phosphoric acid catalyst. This reaction is a rare example of the Friedel–Crafts reaction involving ketimines possessing alkyl substituents, such as isobutyl and isopropyl groups, and is also an attractive method for the synthesis of (thio)hydantoin derivatives which have a quaternary stereogenic center at the 5-position. In addition, theoretical studies were conducted to clarify the origin of the stereochemical outcome as well as the major factors contributing to the efficient enantioselection, which would contribute to developing new enantioselective reactions catalyzed by chiral phosphoric acid.

Acknowledgements

This research was partially supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" from MEXT (Japan) and a Grant-in-Aid for Scientific Research from the JSPS.

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20 In order to experimentally validate the proposed reaction mechanism involving the formation of imine from hemiaminal ethers, we carried out a control experiment. Thus, the possibility of the other reaction mechanism such as the S_N2-type mechanism including dynamic kinetic resolution was examined. Treatment of enantiomerically-pure **4d** with a catalytic amount of achiral diphenyl phosphate, $(PhO)_2P(=O)OH$, provided the corresponding adduct **7d** in a 55% yield in a completely racemic form. This result clearly reveals that the involvement of the S_N2-type mechanism is ruled out and indirectly supports our proposed mechanism. For the kinetic resolution through the S_N2 reaction catalyzed by chiral phosphoric acid, also

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22 The high acidity of the proton at the γ position of the butenolide moiety of **10** allowed the epimerization at that position to proceed easily, even during column purification, and a 2 : 1 diastereomixture was obtained from each attempt for the transformation of **9** to **10** under different reaction conditions. Thus the 2 : 1 ratio is assumed to be thermodynamically determined.

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