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Relationship between the structure and enantioselectivity in the asymmetric reduction of 2′,6′-disubstituted acetophenones with DIP-Chloride^{TM}. An ab initio study

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Abstract—Using computational and chemical studies, a relationship between the % ee achieved and the dihedral angles between the plane of the aromatic ring and the plane containing the carbonyl group has been established for asymmetric reductions with B-chlorodiisopinocampheylborane.

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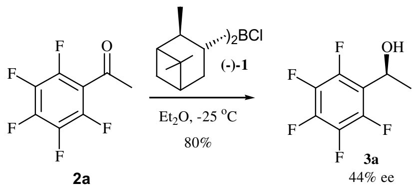
As part of our ongoing projects in fluoroorganic chemistry[1] we attempted the asymmetric reduction of 2′,3′,4′,5′,6′-pentafluoroacetophenone (**2a**) with (−)-DIP-Chloride^{TM})[2] ((−)-**1**) under the usual conditions, Et_2O, 1 M, −25 °C (Eq. 1). Workup using acetaldehyde–aqueous NaOH[3] provided the corresponding product alcohol **3a** in 80% isolated yield. Analysis of this alcohol as its α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA ester)[4] using a SPB-5 capillary column[5] on a gas chromatograph revealed an ee of only 44%! This reagent typically provides ⩾90% ee for most aralkyl ketones, including sterically encumbered ones. A systematic investigation to understand the factors responsible for the low ee has revealed that lower ee and decreased rate of reduction are the norm for 2′,6′-substituted acetophenones. Also, a relationship between the enantiomeric excesses achieved during the reductions and the dihedral angles between the planes of the carbonyl group and the phenyl rings has been established. The details of the investigation follow.



(1)

Comparison of the optical rotation of **3a** with that reported in the literature confirmed the % ee observed by GC analysis and revealed the configuration of the product to be *S*,[6] which is expected from the results of the majority of intermolecular reductions with **(−)-1**.[2] However, the low % ee achieved is atypical. Given the fact that a fluorine atom is isosteric to a hydrogen atom, the poor ee was initially attributed to the electronic influence of the fluorine atoms.

To delineate the electronic factor, the reductions of several fluorinated acetophenones with **(−)-1** were examined. The substitution of fluorine atoms at the 2′-, 3′-, or 4′-position of acetophenone (**2b–d**) showed no effect in the enantioselectivity of the products. We obtained 96–98% ee for the corresponding fluorophenethanols (**3b–d**), very similar to that obtained for the reduction of acetophenone with **1**. Nonetheless, the reduction of difluoroacetophenones was revealing. We obtained very high ee (95–98%) for the corresponding product alcohols (**3e–i**) obtained from the reduction of 2′,3′-, 2′,4′-, 2′,5′-, 3′,4′-, and 3′,5′-difluoroacetophenones

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Keywords: Asymmetric reduction; B-Chlorodiisopinocampheylborane; Aralkyl ketones; Dihedral angles.

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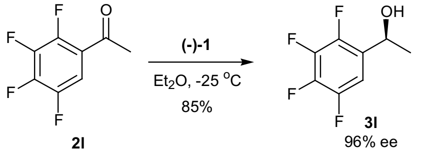
(**2e–i**). However, the reduction of 2′,6′-difluoroacetophenone (**2j**) provided the corresponding product alcohol (**3j**) in only 74% ee. On the basis of (*S*)-**3a**, we believe that we have obtained the *S*-isomer in all of these cases. This showed that the *decrease in enantioselectivity occurred only when both the ortho (2′, and 6′) positions were substituted with fluorine atoms.*

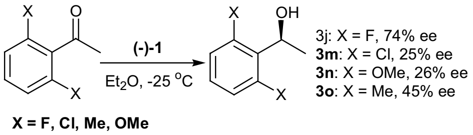
Support for the assumption was provided by the product alcohols **3k** and **3l** obtained from the reduction of 2′,3′,5′-trifluoroacetophenone (**2k**) and 2′,3′,4′,5′-tetrafluoroacetophenone (**2l**) with **1** (Eq. 2). In both of these cases the product alcohols were obtained in 95% and 96% ee, respectively.



2l **3l** 96% ee

(2)

In an unrelated project, we had observed poor ee and very slow rates for the reduction of 2′,6′-substituted acetophenones.[7] For example, 2′,6′-dichloro-(**2m**) and 2′,6′-dimethoxyacetophenone (**2n**) undergoes reduction with **1** only at room temperature (rt) within 2 days and provides the product alcohols in only 25% and 26% ee, respectively (Eq. 3).[8] Relatively, 74% ee obtained for the reduction of 2′,6′-difluoroacetophenone (**2j**) may be attributed to the smaller size of the fluorine atoms as compared to the chlorine atoms or methoxy groups.



3j: X = F, 74% ee
3m: X = Cl, 25% ee
3n: X = OMe, 26% ee
3o: X = Me, 45% ee

(3)

Further support for our hypothesis was obtained from the reduction of 2′,6′-dimethylacetophenone (**2o**) when we obtained 45% ee for the product alcohol (**3o**). Such low ee's are typical of unhindered aliphatic ketones. This comparison led us to believe that the typical high ee's for the product alcohols from aralkyl ketones might be guaranteed only when the ketone is in the plane of the aromatic ring. Losing the planarity between the ring and the carbonyl might force ketones **2m**, **2n**, and **2o** to behave like aliphatic ketones resulting in poor ee for the products. Experimental evidence for this hypothesis was obtained by reducing the corresponding 2′,5′-disubstituted acetophenones. Thus, 2′,5′-dicholoro- (**2p**), 2′,5′-dimethoxy- (**2q**) and 2′,5′-dimethylacetophenone (**2r**) were reduced with **1** when the corresponding alcohols **3p**, **3q**, and **3r** were obtained in 95%, 94%, and 96% ee, respectively. The retarded rate of reduction of 2′,6′-disubstituted acetophenones could be attributed to the sterics around the carbonyl moiety. Slow rate of reduction with **1** is characteristic of hindered ketones.[2]

For a more quantitative analysis, the dihedral angles between the plane of the aromatic ring and the plane containing the carbonyl groups in **2a**, **2j**, **2m**, and **2n** were determined using several computational chemistry methods. Full geometry optimizations were carried out with density functional and ab initio methods. Fully optimized structures were obtained with the Becke 3-parameter functional where the nonlocal correlation is provided by LYP expression (B3LYP) density functional method,[8] and the second-order Moller Plesset (MP2) perturbation method.[9] The ab initio and density functional methods used the 6-31G(d) basis set in all of the calculations.

The dihedral angle in question is represented in Figure 1. The Newman projections showing various dihedral angles are also shown in Figure 1. When viewed along the bond 2–3, the angle is positive if 4 has moved clockwise from 1 and negative if it has moved anticlockwise.

We also compared the dihedral angles of the corresponding 2′-substituted (**2a**, **2s**, **2t**, and **2u**) and 2′,5′-disubstituted acetophenones (**2g**, **2p**, **2q**, and **2r**). The relation between the dihedral angles and the enantiomeric excess of the corresponding alcohols are presented in Table 1. The B3LYP, and MP2 results reveal those ketones exhibiting planarity versus nonplanarity to the plane of the aromatic ring. The calculations show better quantitative agreement between B3LYP and MP2 results for the dihedral angle. When the dihedral angles are compared with % ee, the general trend is that if the ketone is in the plane or very near planarity there is high

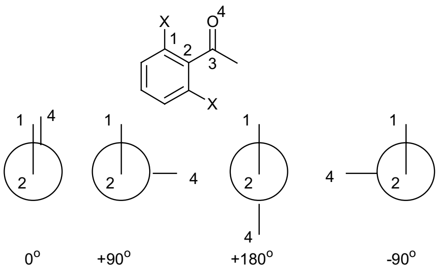


Figure 1. Newman projections showing dihedral angles of substituted acetophenones.

Table 1. Relation between the dihedral angles ring-substituted acetophenones and the enantiomeric excess achieved for reduction with DIP-Chloride™

#	Acetophenone substituent(s)	Dihedral angle		Alcohol	
		B3LYP	MP2	#	% ee
2b	2′-Fluoro	180	−180	**3b**	95
2s	2′-Chloro	160.6	149.4	**3s**	96
2t	2′-Methoxy	−179.9	−179.8	**3t**	92
2u	2′-Methyl	0	0	**3u**	96
2g	2′,5′-Difluoro	−180	−179.9	**3g**	95
2p	2′,5′-Dichloro	149.9	161.4	**3p**	95
2q	2′,5′-Dimethoxy	−179.9	−179.9	**3q**	94
2r	2′,5′-Dimethyl	14.2	0.01	**3r**	96
2l	2′,6′-Difluoro	−26.8	−26.8	**3l**	74
2m	2′,6′-Dichloro	89	89.9	**3m**	25
2n	2′,6′-Dimethoxy	60.8	71.0	**3n**	26
2o	2′,6′-Dimethyl	94.8	112.9	**3o**	45

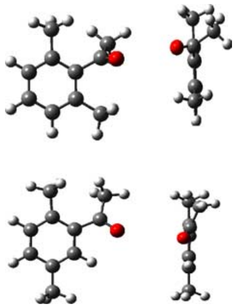


Figure 2. Diagram showing the planes of the carbonyl groups of **2o** and **2q** derived from B3LYP calculations through and perpendicular to the plane of the phenyl ring.

asymmetric induction during the reduction of 2′,6′-disubstituted acetophenones by DIP-Chloride™. The 2′,6′-disubstituted acetophenones are characterized by dihedral angles that are out-of-the plane, particularly for the 2′,6′-dichloro and 2′,6′-dimethylacetophenone, which show dihedral angles close to 90°. In contrast, the dihedral angle for 2′,5′-disubstituted acetophenones revealed a dihedral angle of close to 0° and the reduction of these ketones with **1** provided the products in 92–96% ee. Figure 2 clearly shows the lack of planarity of the carbonyl group of 2′,6′-dimethylacetophenone when compared with that of the 2′,5′-analog.

2′,6′-Difluoroacetophenone show intermediate structure between planarity and nonplanarity by a dihedral angle of 27° at the B3LYP and MP2 levels of theory. An inspection of its % ee is intermediate (74%) between the high % ee of those ring-substituted acetophenones showing planarity and those showing nonplanarity. As can be seen, the larger the deviation from the dihedral angle, the lower is the enantiomeric excess for the product from the reduction of the ketone.

In conclusion, we have carried out a computational study of the dihedral angles between the planes of the carbonyl and aromatic ring of substituted acetophenones. The present experimental and computational results have established a clear relationship between the structure and reactivity (enantioselectivities) achieved in asymmetric reduction of 2′,6′-disubstituted acetophenones with DIP-Chloride™. We are examining the generality of this phenomenon in other asymmetric transformations containing 2′,6′-disubstituted benzene derivatives.

Acknowledgements

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