Stereoselective Syntheses of 3-Substituted Flavene Derivatives and Asymmetric Dehydration *via* Kinetic Resolution

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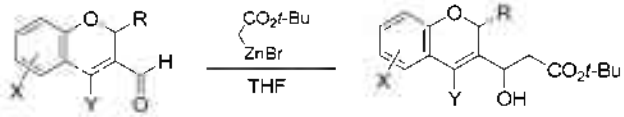
The 2-phenyl-2*H*-chromene structural core is a widespread element in natural flavonoids and has attracted intense attention since a wide range of biological activities associated with the scaffold have been identified.[1] Accordingly, the development of facile synthetic strategies to access such heterocycles is of considerable interest and a few asymmetric synthetic methods have been reported recently.[2] Although the asymmetric methods could provide enantioenriched flavene derivatives, their development for more functionalized flavene skeleton has proven to be a challenging synthetic task. In this communication, we wish to report diastereoselective Reformatsky reaction of flavene-3-carbaldehydes to provide *β*-(2*H*-3-flavenyl)-*β*-hydroxy esters and disclose a new enantioselective synthetic method for 3-substituted flavene derivatives by asymmetric dehydration *via* kinetic resolution.

We have initially investigated the substrate controlled diastereoselective addition of Reformatsky reagent to flavene-3-carbaldehydes **1**, in which the chiral center at the C(2) position of 2*H*-chromene exerts control over the formation of new stereogenic center. In an initial experiment, to a solution of $BrZnCH_2CO_2t$-Bu (3 equiv) in THF was added a solution of flavene-3-carbaldehyde **1a** in THF, and the resulting mixture was heated to reflux to afford the products **2a** and **3a** in 91% yield with a diastereomeric ratio (dr) of 71:29. (entry 1, Table 1) Different experimental conditions have been tested on flavene-3-carbaldehyde **1a** to improve the diastereoselectivity of the addition. Since the diastereoselectivity could be enhanced by effecting the reaction at low temperature, different reaction temperatures have been tested on flavene-3-carbaldehyde **1a** as summarized in Table 1. As the reaction temperature decreases, the dr is improved as shown in entries 1-5. The ratio of major **2a** to minor product **3a** was 79:21 at rt, whereas it was 90:10 at −15 °C. At −30 °C, much slower reaction gave products **2a** and **3a** with only 15% conversion after 5 h and a slightly improved dr of 92:8. (entry 5) Polar solvents were then screened in an attempt to increase the solubility of the reagent and to enhance the rate and the selectivity of the reaction. The use of THF-DMSO (1:1), THF-*p*-dioxane (1:1) and *p*-dioxane respectively as solvent (entries 6-9) did not increase the stereoselection and decreased the yield of the reaction. Under the optimized condition at −15 °C in THF, the reaction of *o*-methoxy substituted flavene aldehyde **1b** gave slightly lower dr (entry 10) and *p*-methoxy substituted flavene aldehydes **1c-e** reacted with Reformatsky reagent leading to **2c-e** and **3c-e** with drs ranging from 89:11 to 91:9, which are practically independent on the presence of the substituents on the aromatic rings and substitution pattern. While 4-chloro substituent increase the selectivity up to 94:6 dr (entry 16), 2-methyl substituted chromenes **1f** and **1g** showed much lower selectivity (entries 14-15).

Non-enzymatic kinetic resolution of racemic compounds using chiral catalyst is an area of great importance in contemporary organic synthesis.[3] We recently reported the first example of the kinetic resolution in dehydration of alcohols using *D*-Phg-*L*-Pro-derived chiral ligand **5**.[4] Given

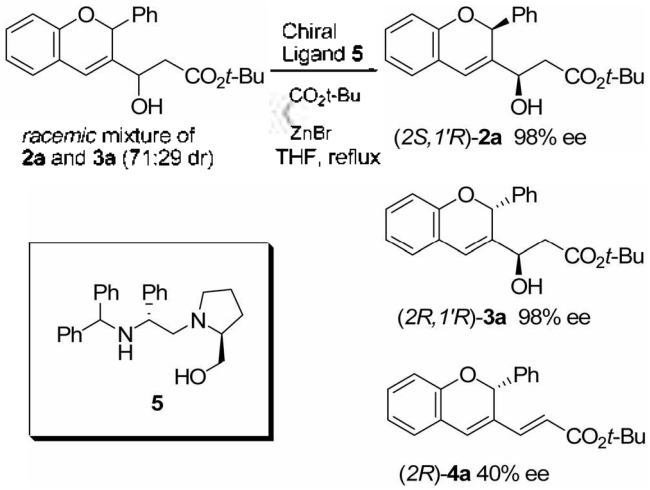
Table 1.



rac-**1a-h** → **2a-h** (major), **3a-h** (minor)

Entry	S.M.	X	Y	R	Condition	Yield[a] (%)	Dr[b] (**2**:**3**)
1	**1a**	H	H	Ph	reflux, 0.5 h, THF	91	71:29
2	**1a**	H	H	Ph	rt, 1 h, THF	88	79:21
3	**1a**	H	H	Ph	0 °C, 2 h, THF	89	87:13
4	**1a**	H	H	Ph	−15 °C, 5 h, THF	81	90:10
5	1a	H	H	Ph	−30 °C, 5 h, THF	11	92:8
6	1a	H	H	Ph	rt, 2 h, THF+DMSO	50	78:22
7	1a	H	H	Ph	rt, 2 h, THF+*p*-Dioxane	52	78:22
8	1a	H	H	Ph	rt, 2 h, *p*-Dioxane	61	83:17
9	1a	H	H	Ph	−15 °C, 6 h, THF+DMSO	50	85:15
10	**1b**	6-Cl	H	*o*-MeO-Ph	−15 °C, 5 h, THF	80	85:15
11	**1c**	6-Cl	H	*p*-MeO-Ph	−15 °C, 5 h, THF	77	89:11
12	**1d**	6-MeO	H	*p*-MeO-Ph	−15 °C, 5 h, THF	79	91:9
13	**1e**	8-MeO	H	*p*-MeO-Ph	−15 °C, 5 h, THF	85	89:11
14	**1f**	H	H	CH_3	−15 °C, 5 h, THF	77	74:26
15	**1g**	6-MeO	H	CH_3	−15 °C, 5 h, THF	72	74:26
16	**1h**	H	Cl	Ph	−15 °C, 5 h, THF	81	94:6

[a]Isolated yields. [b]The drs are determined by ^{1}H NMR of reaction mixture.



Scheme 1

the high levels of selectivity attainable in the asymmetric dehydration of β-aryl or alkenyl β-hydroxy esters with chiral ligand **5**, we evaluated whether β-(2*H*-3-flavenyl)-β-hydroxy esters **2** and **3**, which bear an additional stereogenic center, might be good candidates for kinetic resolution with the chiral ligand. When the diastereomeric mixture of racemic **2a** and **3a** (71:29 dr) was treated with $BrZnCH_2CO_2$-*t*-Bu and chiral ligand **5** (5 mol%) in refluxing THF for 3 h, the dehydrated product **4a** was isolated in 49% yield (59% conversion) and unconverted diastereomeric mixture of **2a** and **3a** was obtained in 29% combined yield.[5] The dr of unreacted esters **2a** and **3a** was 70:30 as determined by analysis of the ^{1}H NMR spectrum of reaction mixture and enantiomeric excess (ee) was 98% for each one. With chiral ligand **5**, both **2a** and **3a** were dehydrated at similar rates and kinetically resolved with similar efficiencies, producing the eliminated product **4a** with 40% ee. These results reflect highly effective discrimination between 1'*S* and 1'*R* chiral center in dehydration, but little influence of the chiral center at 2-position.

To determine the stereochemical relationship of the diastereomers **2a** and **3a**, we have carried out the reaction of the mixture of enantioenriched (2*R*)-**2a** and (2*R*)-**3a** under the same condition with chiral ligand **5**.[6] The chiral phase HPLC analysis of the reaction mixture indicates that (2*R*)-**2a** is a fast reacting enantiomer of **2a**, while (2*R*)-**3a** is a slow reacting enantiomer of **3a**. Based on the assumption that the 1'*S* enantiomer is dehydrated faster than 1'*R* enantiomer with chiral ligand **5**,[7] the absolute configurations of slow reacting enantiomers of **2a** and **3a** are provisionally assigned as (2*S*,1'*R*) and (2*R*,1'*R*) respectively as indicated in Scheme 1.

We here reported the highly diastereoselective Reformatsky reactions and successful catalytic kinetic resolution of β-(2*H*-3-flavenyl)-β-hydroxy esters in asymmetric elimination. To our knowledge, this is the first highly enantioselective method to prepare 3-alkenyl flavenes and 3-(1-hydroxyalkyl) flavenes containing two stereogenic centers. These products contain several functionalities that allow further transformations into more complex molecules. Further investigation of the scope of the asymmetric elimination with various β-(2*H*-3-flavenyl)-β-hydroxy esters and its application to the syntheses of biologically interesting molecules is underway.

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References and Notes

1. (a) Satoh, Y.; Stanton, J. L.; Hutchison, A. J.; Libby, A. H.; Kowalski, T. J.; Lee, W. H.; White, D. H.; Kimble, E. F. *J. Med. Chem.* **1993**, *36*, 3580. (b) Cheng, J.-F.; Ishikawa, A.; Ono, Y.; Arrhenius, T.; Nadzan, A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3647. (c) Hajela, K.; Pandey, J.; Dwivedy, A.; Dhar, J. D.; Sarkhel, S.; Maulik, P. R.; Velumurugan, D. *Bioorg. Med. Chem.* **1999**, *7*, 2083. (d) Ishizuka, N.; Matsumura, K.-i.; Kikuchi, J.; Nakai, H. *Bioorg. Med. Chem.* **2002**, *10*, 3965. (e) Funk, O. F.; Kettmann, V.; Drimal, J.; Langer, T. *J. Med. Chem.* **2004**, *47*, 2750. (f) Ishizuka, N.; Matsumura, K.-i.; Sakai, K.; Fujimoto, M.; Mihara, S.-i.; Yamamori, T. *J. Med. Chem.* **2002**, *45*, 2041.
2. (a) Sunden, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Chem. Eur. J.* **2007**, *13*, 574. (b) Li, H.; Wang, J.; E-Nunu, T.; Zu, L.; Jiang, W.; Wei, S.; Wang, W. *Chem. Commun.* **2007**, 507. (c) Govender, T.; Hojabri, L.; Moghaddam, F. M.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2006**, *17*, 1763. (d) Konoike, T.; Matsumura, K.-i.; Yorifuji, T.; Shinomoto, S.; Ide, Y.; Ohya, T. *J. Org. Chem.* **2002**, *67*, 7741. (e) Hardouin, C.; Burgaud, L.; Valleix, A.; Doris, E. *Tetrahedron Lett.* **2003**, *44*, 435.
3. (a) Robinson, D. E. J. E.; Bull, S. D. *Tetrahedron: Asymmetry* **2003**, *14*, 1407. (b) Keith, J. M.; Larrow, J. F.; Jacobson, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5. (c) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **2003**, *125*, 4166. (d) Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 5091. (e) Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629. (f) Mazet, C.; Roseblade, S.; Köhler, V.; Pfaltz, A. *Org. Lett.* **2006**, *8*, 1879. (g) Yamada, S.; Misono, T.; Iwai, Y. *Tetrahedron Lett.* **2005**, *46*, 2239. (h) Suzuki, Y.; Yamauchi, K.; Muramatsu, K.; Sato, M. *Chem. Commun.* **2004**, 2770.
4. (a) Kim, Y.; Choi, E. T.; Lee, M. H.; Park, Y. S. *Tetrahedron Lett.* **2007**, *48*, 2833. (b) Choi, E. T.; Lee, M. H.; Kim, Y.; Park, Y. S. *Tetrahedron* **2008**, *64*, 1515.
5. *General procedure for asymmetric dehydration:* Trimethylchlorosilane (0.5 equiv) was added to a suspension of zinc metal (8 equiv) in anhydrous THF. After the mixture was refluxed for 40 min, a solution of chiral ligand (5 mol%), *tert*-butyl bromoacetate (8 equiv) and racemic **2a** and **3a** in THF was slowly added. The mixture was stirred at reflux for 2-6 h and then quenched with saturated NH_4Cl aqueous solution. The resulting mixture was extracted with CH_2Cl_2 (2 · 5 mL) and combined extracts were washed with brine. The solvents were removed under reduced pressure and the residue was purified by flash column chromatography to give enantioenriched flavene derivatives.
6. The enantioenriched (2*R*)-**2a** (80:20 er) and (2*R*)-**3a** (80:20 er) were prepared from Reformatsky reaction of (*R*)-flavene aldehyde **1a** (80:20 er), which was prepared by the known procedure with a organocatalyst, (*S*)-diphenylpyrrolinol silyl ether.[2a-c]
7. We have previously reported that asymmetric dehydration of various β-aryl or alkenyl β-hydroxy *t*-butyl esters proceeds favoring (*S*)-enantiomer in the presence of chiral ligand **5**.[4]