Rearrangements Hot Paper

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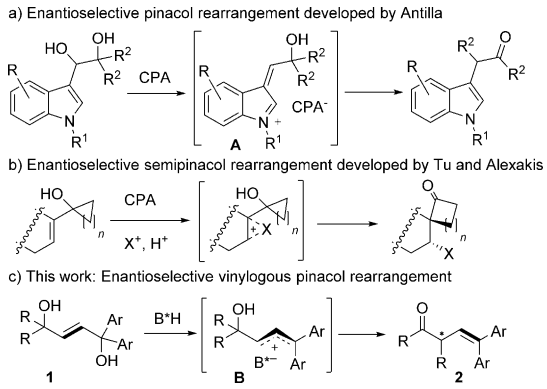
Organocatalytic Enantioselective Vinylogous Pinacol Rearrangement Enabled by Chiral Ion Pairing

*Hua Wu, Qian Wang, and Jieping Zhu**

Abstract: *An enantioselective pinacol rearrangement of functionalized (E)-2-butene-1,4-diols was developed. In the presence of a catalytic amount of a chiral BINOL-derived N-triflyl phosphoramide, these 1,4-diols rearranged to β,γ-unsaturated ketones in excellent yields and enantioselectivities. The formation of a chiral ion pair between the intermediary allylic cation and the chiral phosphoramide anion was postulated to be responsible for the highly efficient chirality transfer. These chiral building blocks were further converted into enantioenriched polysubstituted tetrahydrofuran and tetrahydronaphthalene derivatives.*

Pinacol rearrangements, which convert 1,2-diols into ketones under acidic conditions, are a blueprint for a group of carbenium-based molecular reorganization processes.[1] As such reactions generate a new stereogenic center, the ability to control the stereochemical outcome would significantly expand their synthetic utility. However, several factors intrinsic to the reaction mechanism have made this endeavor highly demanding. First, the regioselective generation of one of the two possible carbenium intermediates under strongly acidic conditions is difficult. Second, differentiation of the prochiral faces of highly reactive planar carbocation intermediates is a formidable challenge as it falls out of the reach of typical Lewis acid and Brønsted acid catalysis. As a matter of fact, Antilla's chiral phosphoric acid (CPA) catalyzed rearrangement of indolyl diols is the only example of an enantioselective pinacol rearrangement to date (Scheme 1 a).[2] In this transformation, the benzylic cation is generated regioselectively and stabilized in the form of conjugated iminium species **A**,[3] thereby facilitating the transfer of chiral information. Indeed, imines are the most widely exploited substrates in CPA-catalyzed asymmetric transformations.[4,5]

To circumvent the aforementioned challenges, a number of efficient catalytic enantioselective semipinacol rearrangements have been developed.[6–8] Two key structural elements have been strategically incorporated into the substrates of these reactions in order to a) regioselectively generate the cationic intermediate or its equivalent and b) render the 1,2-C–C bond shift a ring-strain-releasing process (Scheme 1 b). While the synthetic significance of these transformations is self-evident, constraints imposed on the substrate structure have nevertheless limited the full exploitation of the pinacol rearrangement. In connection with our ongoing studies of organocatalytic enantioselective transformations,[9] we became interested in the chiral contact ion pairs[10] formed between a CPA and cationic intermediates other than iminium species,[11,12] and we chose allylic cations[13] as our playground. We herein report a catalytic enantioselective vinylogous pinacol rearrangement of 1,4-diols **1** to β,γ-unsaturated ketones **2** (Scheme 1 c) and provide evidence that supports the hypothesis that chiral allylic contact ion pair **B** is a key intermediate for the transfer of chirality. The vinylogous pinacol rearrangement is known[14] and has been utilized in complex natural product synthesis.[15] However, its asymmetric version was still unknown at the outset of this work.



Scheme 1. Chiral Brønsted acid catalyzed pinacol rearrangements.

(*E*)-1,1-Bis(4-methoxyphenyl)-4,4-diphenylbut-2-ene-1,4-diol (**1a**) was chosen as the model substrate. In the presence of chiral phosphoric acid (*S*)-**3a** (0.1 equiv), **1a** underwent a pinacol rearrangement to afford β,γ-unsaturated ketone **2a** as the only detectable regioisomer in 42% yield with 22% *ee* (Table 1, entry 1). Other CPAs such as TRIP (**3b**, entry 2) and STRIP (**3c**, entry 3) failed to improve the reaction outcome. However, a dramatic increase in yield was observed when *N*-triflyl phosphoramides (Figure 1),[16] which are stronger Brønsted acids, were used as catalysts, with **3f** providing the best result (entries 4–7). Using **3f** as the catalyst, the reaction conditions were further optimized by varying the solvent, additive, and reaction temperature. Importantly, adding 4 Å molecular sieves (M.S.) significantly increased the yield and enantiopurity of the product. Overall, the best conditions consisted of performing the reaction in methyl *tert*-butyl ether

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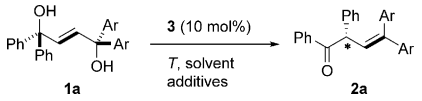
Table 1: Optimization of the reaction conditions.[a]



Entry	B*-H	Solvent	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	**3a**	toluene	25	42	22
2	**3b**	toluene	25	52	28
3	**3c**	toluene	25	35	25
4	**3d**	toluene	25	95	10
5	**3e**	toluene	25	92	12
6	**3f**	toluene	25	97	38
7	**3g**	toluene	25	98	11
8	**3f**	toluene	−20	92	56
9	**3f**	DCM	−20	94	74
10	**3f**	THF	−20	72	65
11	**3f**	CH_3NO_2	−20	68	4
12	**3f**	Et_2O	−20	71	84
13[d]	**3f**	Et_2O	−20	95	89
14[d]	**3f**	DME	−20	96	90
15[d]	**3f**	**MTBE**	**−20**	**99**	**91**
16[d]	**3f**	MTBE	−40	94	91

[a] Reaction conditions: **1a** (0.05 mmol, Ar = 4-MeOC$_6$H$_4$), B*-H (0.005 mmol), solvent (1.0 mL), 12 h. [b] Yield of isolated product. [c] Determined by supercritical fluid chromatography on a chiral stationary phase. [d] 4 Å molecular sieves (40 mg) were added. DCM = dichloromethane, DME = 1,2-dimethoxyethane.

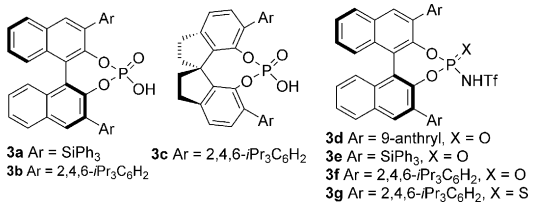
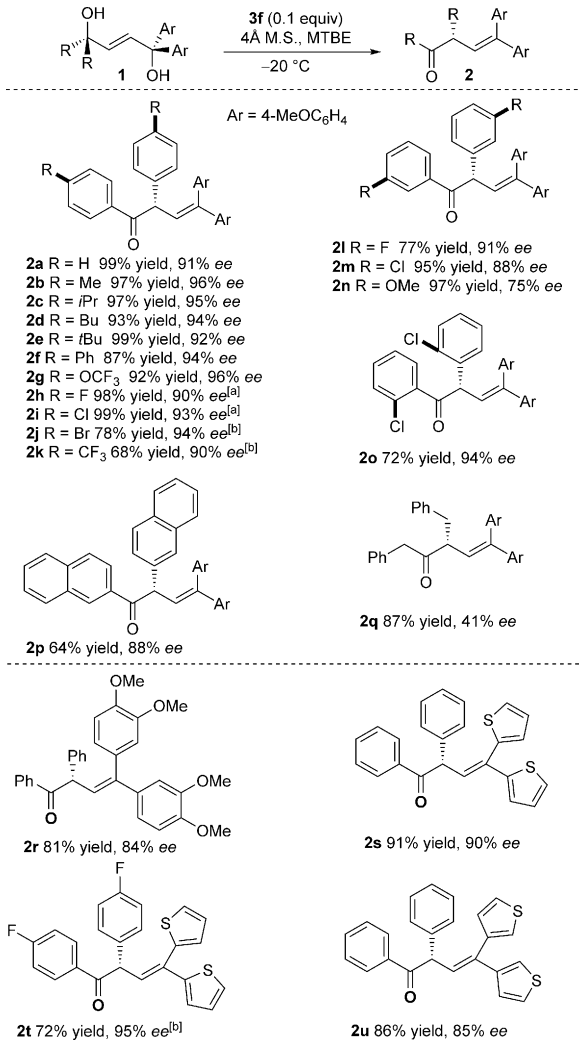


Figure 1. Structures of representative CPAs and chiral phosphoramides.



Scheme 2. Scope of the vinylogous pinacol rearrangement. [a] At room temperature. [b] At 0 °C.

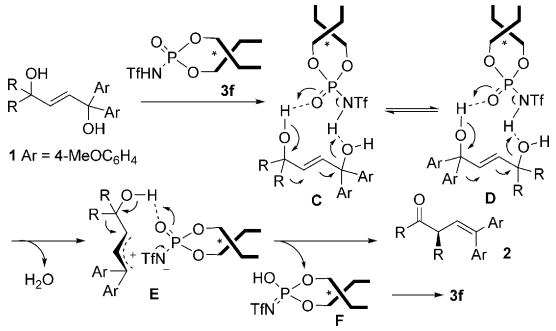
(MTBE, 0.05 M) at −20 °C in the presence of **3f** (0.1 equiv) and 4 Å molecular sieves. Under these conditions, ketone **2a** was isolated in 99 % yield with 91 % *ee* (entry 15).[17]

Next, the scope of this vinylogous pinacol rearrangement was examined. A variety of substrates bearing electron-rich, electron-neutral, and electron-deficient aryl moieties underwent the desired regioselective rearrangement to generate β,γ-unsaturated ketones **2** in high yields with excellent enantioselectivities (Scheme 2). Substituents at the *para*, *meta*, and *ortho* positions were well tolerated (**2a**–**2o**). Electron-poor aromatic moieties migrated equally well upon conducting the reaction at 0 °C or at room temperature (**2h**–**2m**, **2o**). A naphthyl-substituted 1,4-diol participated in this asymmetric 1,2-shift process to provide **2p** in good yield and enantioselectivity. Finally, a benzyl-substituted 1,4-diol afforded the corresponding product **2q** in excellent yield, albeit with diminished enantioselectivity.

It is clear that the 4-methoxyphenyl group very efficiently controls the regioselective generation of the carbenium intermediate. Pleasingly, other substituents that are capable of stabilizing the cationic intermediate, such as 3,4-dimethoxyphenyl as well as 2- and 3-thiophene moieties, can play the same role to afford the corresponding enantioenriched ketones (**2r**–**2u**) in excellent yields with high enantioselectivities.

On gram scale, the rearrangement reaction of **1a** also proceeded smoothly to afford **2a** in 89 % yield with 87 % *ee*. Recrystallization (CH_2Cl_2/MeCN) furnished the desired product in enantiopure form. The absolute configuration of **2a** was determined by X-ray crystallography,[18] and the configurations of the other β,γ-unsaturated ketones were assigned accordingly.

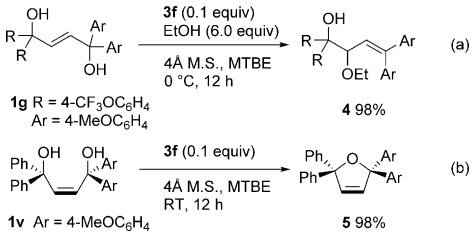
A possible reaction pathway is depicted in Scheme 3. Hydrogen bonding between 1,4-diol **1** and *N*-triflyl phosphoramide **3f** should generate two possible intermediates **C** and **D**, which might be in equilibrium. It was assumed that dehydration of **C** leading to allylic cation/chiral phosphoramide anion pair **E** would be a kinetically faster process than dehydration of **D** owing to the resonance contribution of the 4-methoxy group in **E**. Therefore, the reaction would be pulled towards the formation of ion pair **E** following the Curtin–Hammett principle, which leads to the observed high regioselectivity of the rearrangement process. A subsequent



Scheme 3. Possible reaction pathway for the regio- and enantioselective vinylogous pinacol rearrangement of 1,4-diols.

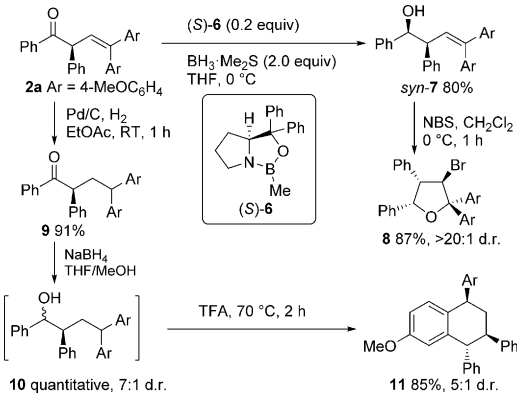
enantioselective 1,2-shift of the R group in **E**, assisted by the chiral phosphoramide anion, would produce the enantioenriched ketone **2** with concurrent release of **F**, which, upon tautomerization, would regenerate catalyst **3f**. The importance of the resonance contribution of the methoxy group is readily seen in the conversion of **1n** into **2n**, which results from the selective migration of the 3-methoxyphenyl group at the expense of the 4-methoxyphenyl group.[19]

A series of experiments were performed to support the proposed mechanism of this enantioselective pinacol rearrangement. First, submitting racemic β,γ-unsaturated ketone **2a** to our standard reaction conditions led only to the recovery of (±)-**2a** without any enantioenrichment. Therefore, the formation of enantioenriched **2a** did not occur by a non-stereoselective pinacol rearrangement to (±)-**2a** followed by CPA-catalyzed enantioselective protonation of its enol form.[20] Second, performing the reaction of **1g** in the presence of EtOH (6.0 equiv) under otherwise identical conditions afforded ethoxylated product **4** in racemic form and 98% yield (Scheme 4a). Should the reaction proceed



Scheme 4. Control experiments.

through an S_N2' mechanism, rearrangement via postulated transition state **C** (or **D**) should be competitive, leading to product **2g**. Furthermore, if the reaction indeed proceeded through an S_N2' mechanism, migration of the electron-rich aryl group (4-methoxyphenyl), which has a higher migratory aptitude, via TS **D** would dominate, leading to an isomer of **2g**. However, these scenarios did not occur under our conditions. Finally, the reaction of (*Z*)-2-butene-1,4-diol **1v** under our standard conditions provided dihydrofuran **5** in 98% yield, indicating that in this case, the ring closure is much faster than the double-bond isomerization via the allylic cation (Scheme 4b).[21]



Scheme 5. Synthetic transformations of chiral β,γ-unsaturated ketone **2a**.

Further transformations of β,γ-unsaturated ketone **2a** were performed to illustrate the synthetic potential of our reaction (Scheme 5). Chemoselective CBS reduction[22] with catalyst (*S*)-**6** afforded *syn*-**7** and its *anti* isomer in yields of 80% and 11%, respectively. Treatment of diastereomerically pure *syn*-**7** with *N*-bromosuccinimide (NBS)[23] afforded tetrahydrofuran **8**, an analogue of sacidumlignan D,[24] in 87% yield. Hydrogenation of **2a** (Pd/C, H_2, EtOAc) furnished saturated ketone **9** in 91% yield. Reduction of **9** with sodium borohydride produced intermediate **10** as a mixture of two diastereomers (7:1 d.r.). Friedel–Crafts cyclization of **10** in trifluoroacetic acid (TFA)[25] then provided tetrahydronaphthalene **11** in 87% yield (5:1 d.r.).[26]

In conclusion, we have developed the first enantioselective vinylogous pinacol rearrangement of 1,4-diols catalyzed by a chiral *N*-triflyl phosphoramide. The formation of a chiral contact ion pair between the intermediary allylic cation and the conjugated base of the chiral Brønsted acid was proposed to be responsible for the observed enantioselectivity. The utility of this transformation was illustrated by the subsequent conversion of the resulting β,γ-unsaturated ketones into enantioenriched polysubstituted tetrahydrofuran and tetrahydronaphthalene derivatives.

Acknowledgements

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Keywords: chiral Brønsted acids · 1,4-diols · ion pairs · organocatalysis · pinacol rearrangements

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[18] CCDC 1487213 (**2a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[19] Treatment of symmetric (*E*)-1,1,4,4-tetrakis(4-methoxyphenyl)-but-2-ene-1,4-diol (**1w**) under the standard conditions afforded rearranged product **2w** in 97% yield with 26% *ee* (see the Supporting Information). Migration of the Ar group of high migratory aptitude before formation of the contact ion pair, and hence low chiral communication, could be responsible for the low enantioselectivity.
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Communications

Rearrangements

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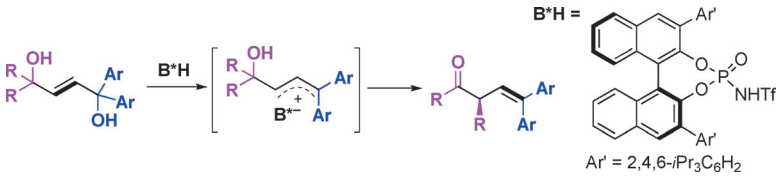

Pair and reorganize: In the presence of a chiral BINOL-derived *N*-triflyl phosphoramide, functionalized (*E*)-2-butene-1,4-diols undergo an enantioselective pinacol rearrangement to β,γ-unsaturated ketones. The formation of a chiral contact ion pair between the allylic cation and the conjugated base of the chiral Brønsted acid might be responsible for the observed enantioselectivity.