Enantioselective Synthesis of Tropanes: Brønsted Acid Catalyzed Pseudotransannular Desymmetrization

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Angew. Chem. Int. Ed. **2020**, *59*, 6780.

DOI: **10.1002/anie.202000650**

Enantioselective Synthesis of Tropanes through Brønsted Acid-Catalyzed Pseudotransannular Desymmetrization

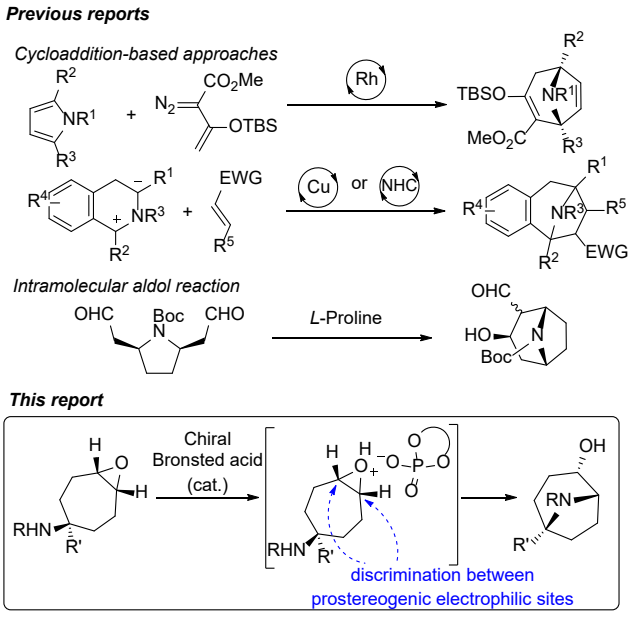
Sandra Rodriguez,[a] Uxue Uria,*[a] Efraim Reyes,[a] Luisa Carrillo,[a] Tomás Tejero,[b] Pedro Merino*[c] and Jose L. Vicario*[a]

Dedication ((optional))

Abstract: The enantioselective synthesis of tropanols has been accomplished through chiral phosphoric acid-catalyzed pseudotransannular ring-opening of 1-aminocyclohept-4-ene-derived epoxides. The reaction proceeds together with the desymmetrization of the starting material and leads to the direct formation of the 8-azabicyclo[3.2.1]octane scaffold with excellent stereoselectivity. The synthetic applicability of the reaction has been demonstrated through the enantioselective synthesis of two natural products such as (-)-α-tropanol and (+)-ferruginine.

Tropane alkaloids are members of a family of natural products with a wide variety of biological activities, most of them biochemically related to the interactions with the cell receptors of the neurotransmitter acetylcholine.[1] From the landmark synthesis of tropinone by Robinson in 1917,[2] a variety of different synthetic approaches to the central 8-azabicyclo[3.2.1]octane molecular architecture of the tropane alkaloids have been developed.[3] In particular, and considering that several members of this family occur as chiral compounds, efficient approaches to the asymmetric synthesis of the tropane scaffold are also required for a fast access to new analogues with novel or improved potential applications in drug discovery programs. Despite the intense effort carried out for many decades, most of the stereoselective approaches to chiral tropanes still rely on diastereoselective reactions that make use of enantioenriched starting materials[4] or, alternatively, focus on the desymmetrization of achiral tropinone derivatives.[5] In fact, enantioselective methodologies in which the stereochemical information is installed on the same reaction in which the 8-azabicyclo[3.2.1]octane scaffold is generated are particularly scarce. Specifically, the only few reports dealing with catalytic and enantioselective reactions generating the tropane framework include the pioneering formal (4+3) cycloaddition between pyrroles and enol diazoacetates under chiral Rh(II) catalysis reported by Davies and Reddy,[6] several examples of enantioselective 1,3-dipolar cycloadditions involving isoquinoline-based cyclic azomethine ylides,[7] and the *L*-proline-catalyzed intramolecular aldol reaction of *meso*-*N*-Boc-(pyrrolidine-2,5-diyl)diacetaldehyde (see Scheme 1).[8]

In view of these precedents, we envisaged an alternative enantioselective approach to 8-azabicyclo[3.2.1]octanes through intramolecular ring-opening of *meso* cycloalkenylamine-derived epoxides under Brønsted acid catalysis (Scheme 1). In particular, we worked under the hypothesis that a chiral BINOL-based phosphoric acid or related derivative[9] should be able to discriminate between the two chemically equivalent prostereogenic electrophilic carbon atoms of the epoxide moiety,[10] leading to the formation of a single enantiomer in an overall desymmerization process. The construction of the tropane scaffold from functionalized cycloalkylamines through intramolecular enantiospecific S_N2 displacement has been widely explored in the literature,[11] but this pathway requires substrates in which the stereochemical information has been previously established during the preparation of the starting materials.



Scheme 1. Catalytic and enantioselective approaches to the tropane scaffold.

We initially evaluated the performance of a family of different chiral BINOL-based phosphoric acids as catalysts in the reaction (see Table 1) using epoxycycloheptylamine **1a** as model substrate and working in CH_2Cl_2 at 0ºC (entries 1-6). In these experiments, we observed that the archetypical TRIP catalyst **3a** (entry 1) and a variety of related 3,3'-bis(aryl) substituted BINOL-based phosphoric acids **3b-e** (entries 2-5) were able to promote

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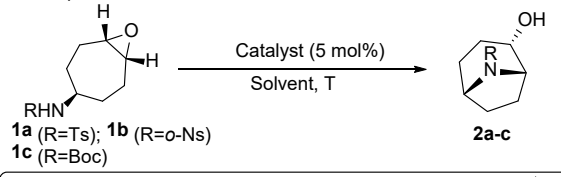
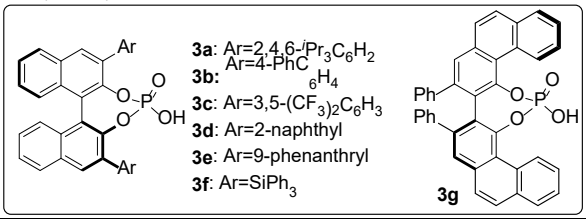
the reaction efficiently and with remarkably low catalyst loading of 5 mol%, although providing poor enantioselectivity. Results did not improve when a spherical and bulkier $SiPh_3$ substituent was placed at this 3,3'-position of the catalyst architecture (entry 6). On the other hand, VAPOL-phosphoric acid **3g** provided **2a** with good yield and a promising 89:11 e.r. (entry 7).

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





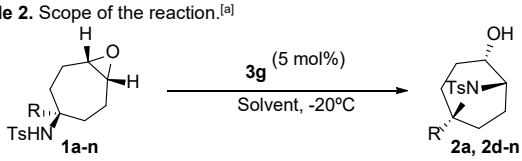
Entry	Cat.	Solvent	R	T [ºC]	Time	Yield [%][b]	e.r.[c]
1	**3a**	CH_2Cl_2	Ts	0	4 h	65	57:43
2	**3b**	CH_2Cl_2	Ts	0	4 h	86	65:35
3	**3c**	CH_2Cl_2	Ts	0	4 h	87	56:44
4	**3d**	CH_2Cl_2	Ts	0	4 h	77	62:38
5	**3e**	CH_2Cl_2	Ts	0	4 h	89	51:49
6	**3f**	CH_2Cl_2	Ts	0	4 h	52	65:35
7	**3g**	CH_2Cl_2	Ts	0	2.5 h	86	89:11
8	**3g**	$CHCl_3$	Ts	0	4 h	80	85:15
9	**3g**	$ClCH_2CH_2Cl$	Ts	0	1 h	95	90:10
10	**3g**	AcOEt	Ts	0	6 h	90	93:7
11	**3g**	Toluene	Ts	0	3 h	98	95:5
12	**3g**	PhCl	Ts	0	3 h	93	94:6
13	**3g**	Toluene	Ts	-20	12 h	95	97:3
14	**3g**	PhCl	Ts	-20	12 h	91	96:4
15[d]	**3g**	Toluene	Ts	-20	12 h	91	98:2
16	**3g**	Toluene	*o*-Ns	-20	7 d	38	94:6
17	**3g**	Toluene	Boc	-20	24 h	<5	n.d.[e]

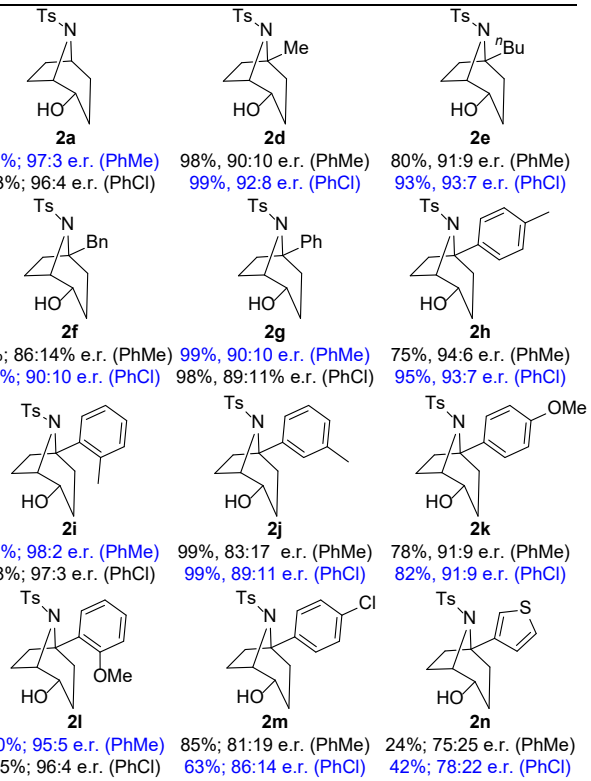
[a] All reactions were carried out at 0.05 mmol scale of **1a-c**, using 5 mol% of catalyst in 0.05 mL of solvent at the indicated temperature until consumption of starting material was observed (TLC analysis). [b] Yields refer to isolated pure product **2a-c**. [c] Calculated by HPLC on chiral stationary phase (see supporting information for details). [d] 2.5 mol% of catalyst **3g** was used. [e] n.d. not determined.

Fine-tuning of reaction conditions was carried out using this catalyst as the best performing one, which included changing the solvent and temperature (entries 8-14). In particular, other halogenated solvents like $CHCl_3$ or 1,2-dichloroethane performed slightly better compared to CH_2Cl_2 (entries 8 and 9 vs 7), but changing to AcOEt (entry 10) led to a very effective reaction, isolating **2a** in high yield and 93:7 e.r., although requiring a longer reaction time. The use of toluene (entry 11) or the greener PhCl solvent (entry 12) also resulted in a reaction with a similar efficiency but requiring only 3h. The catalyst loading could be decreased to 2.5 mol% without any significant decrease in the yield (entry 15). Finally, substrates **2b-c** containing different *N*-substituents were tested (entries 16-17) at -20 ºC, observing that the reaction did not afford better results.

With an optimized experimental protocol in hand, we next proceeded to evaluate the scope and limitations of this transformation with respect to its applicability towards the enantioselective synthesis of a variety of related tropane scaffolds. In all cases the reactions were tested using toluene and chlorobenzene, with slight differences observed between both solvents but in all cases providing one entry that performs slightly better than the other (highlighted in blue).

Table 2. Scope of the reaction.[a]





[a] All reactions were carried out at 0.05 mmol scale of **1**, using 5 mol% of **3g**, in 0.18 mL of toluene or PhCl at -20ºC. Yields refer to isolated pure product calculated taking into account unreacted diastereoisomer impurities present on starting material and e.r. was calculated by HPLC on chiral stationary phase (See supporting information for details).

As it can be seen in table 2, the reaction proceeded well with a variety of *meso*-4,5-epoxycycloheptylamines containing different alkyl substituents at 1-position, including the small methyl

substituent (compound **2d**) or longer alkyl substituents (compounds **2e** and **2f**). Aryl moieties at this position were also well tolerated, also enabling the incorporation of substituents with diverse electronic nature at different positions in the aryl ring (compounds **2g-m**). An example incorporating a heteroaromatic moiety such as the 2-thienyl substituent was also tested but the yield of **2n** was significantly lower. It has to be pointed out that, in some cases, it was not possible to operate with diastereomerically pure samples of the aminoepoxide starting materials **1** and therefore, in those cases in which diastereomeric mixtures of 1,5-*cis*- and 1,5-*trans*-aminoepoxides **1** had to be used, corrected yields based on recovered unreacted 1,5-*cis* isomer are given. The absolute configuration of the adducts obtained by this protocol was established by single-crystal X-ray analysis of an enantiopure sample of compound **2a**, for which a monocrystal could be obtained.[12] Accordingly to the stereostructure obtained for this compound, the configuration of all other adducts **2a-n**, was established by assuming the same stereochemical outcome for all reactions based on mechanistic analogy.

We also carried out a computational study directed to a better understanding of the reaction pathway. The reaction showed a typical S_N2 mechanism in which the H-transfer from nitrogen to oxygen atoms is promoted by the catalyst, facilitating the epoxide opening. We located the two possible transition structures leading to (*S,S,R*)-**2a** and (*R,R,S*)-**2a** (Figure 1, top). A difference of 3.4 kcal/mol in favor of (*S,S,R*)-**TS** (predicted e.r.: 99.7:0.3) was observed, in good agreement with the experimental findings. The optimized geometries for the transition structures showed a shorter forming bond (2.33 Å) for the preferred (*S,S,R*)-**TS** than for the less favored (*R,R,S*)-**TS** (2.79 Å).

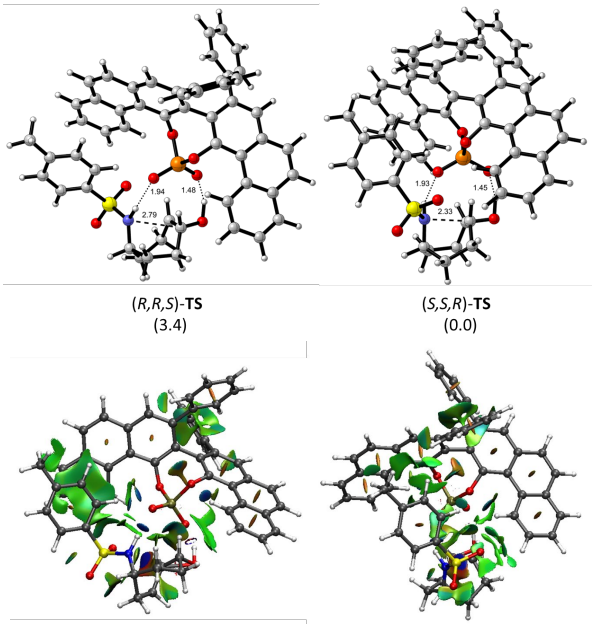
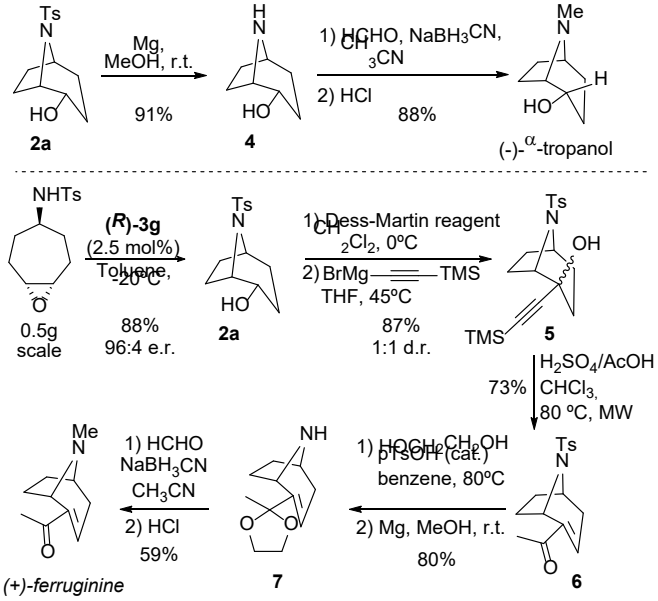


Figure 1. Top: Optimized (b3lyp-d3bj/def2svp) geometries of transition structures. Bottom: NCI calculations (blue: strong; green: weak; red: repulsive).

We have also carried out a topological analysis of non-covalent interactions (NCI)[13] (Figure 1, bottom) and, interestingly, we found that the transition structure presenting London interaction between the catalyst and the tosyl group was not the preferred one, in contrast with previous observations for this type of catalysts.[14] The ultimate reason of the higher stability observed for (*S,S,R*)-TS is the presence of favorable interactions between the C-H adjacent to the nitrogen atom and the sulfonyl group of the tosyl moiety. According to the NCI analysis these interactions are stronger than the observed London interactions in (*R,R,S*)-**TS**.

Finally, we also decided to demonstrate the potential of this methodology as a general tool for the total synthesis of different alkaloids from the tropane family (Scheme 2). For instance, the access to (-)-α-tropanol, a derivative with a remarkable array of interesting biological activities,[15] was straightforward from adduct **2a** through simple *N*-detosylation followed by *N*-methylation. On the other hand, the enantioselective total synthesis of (+)-ferruginine, a potent neurotoxin isolated from the arboreal species *Darlingiana ferruginea* and *D. darlingiana*,[16] could be accomplished following the short synthetic route depicted on Scheme 2. In this sense, we initially demonstrated that the catalytic enantioselective desymmetrization of starting material **1a** could be carried out on a larger scale in high yield and enantioselectivity under the optimized conditions. Subsequently, oxidation of the alcohol followed by alkynylation provided intermediate **5** which was subjected to Rupe rearrangement,[17] providing the required enone moiety in a very efficient manner. (+)-Ferruginine was finally obtained after detosylation/*N*-methylation, which implied a previous protection of the ketone functionality as the corresponding acetal and a final deprotection of such enone during the workup of the *N*-methylation step.



Scheme 2. Enantioselective total synthesis of (-)-α-tropanol and (+)-ferruginine.

In conclusion, we have shown that chiral phosphoric acids are very appropriate catalysts for the desymmetrization of 1-aminocyclohept-4-ene-derived epoxides, leading to the formation of tropanes in high yield, diastereo- and enantioselectivity. The excellent performance of this reaction has been demonstrated

with the total synthesis of two examples of bioactive members of this family of alkaloids such as (-)-α-tropanol and (+)-ferruginine. Moreover, mechanistic investigations based both in experimental results and in computational studies show that the presence of a tosyl protecting group at the nitrogen atom is crucial for the success of the reaction due to the requirement of an acidic NH moiety at the pronucleophilic site and also due to the contribution of stabilizing C-H···O=S interactions in the transition state that leads to the major enantiomer.

Acknowledgements

This research was supported by the Spanish MCIU (FEDER-CTQ2017-83633-P, FEDER-CTQ2016-76155-R and FPU fellowship to S. R.), Basque Government (IT908-16) and Government of Aragón (Grupos Consolidados, E.10). The authors thankfully acknowledge the resources from the supercomputers "Memento" and “Cierzo”, technical expertise and assistance provided by BIFI-ZCAM (Universidad de Zaragoza, Spain)

Keywords: Asymmetric catalysis · Desymmetrization · Brønsted Acids · Alkaloids · Organocatalysis

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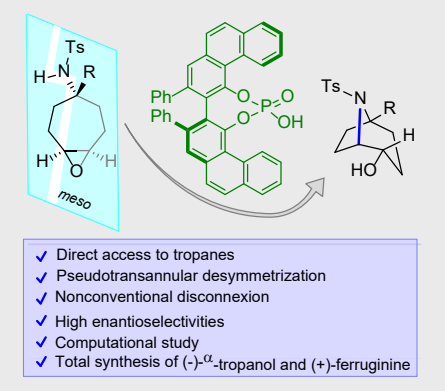
Layout 1:

COMMUNICATION

The VAPOL-phosphoric acid catalysed pseudotransannular epoxide ring opening on *meso* cycloalkenylamine-derived epoxides delivers highly enantioenriched tropanol derivatives in a single step through a very efficient desymmetrization process. This strategy has also been applied to the total synthesis of two naturally occurring alkaloids such as (-)-α-tropanol and (+)-ferruginine.



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