Strong and Confined Acid Catalysts Impart Stereocontrol onto the Non-Classical 2-Norbornyl Cation

Authors: Roberta Properzi,¹ Philip S. J. Kaib,¹ Markus Leutzsch,¹ Gabriele Pupo,¹ Raja Mitra,¹† Chandra Kanta De,¹ Peter R. Schreiner,² Benjamin List¹*

Affiliations:

¹ Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, D-45470 Mülheim an der Ruhr, Germany.
² Institute of Organic Chemistry, Justus Liebig University, Heinrich-Buff-Ring 17, D-35392 Giessen, Germany.
† Present address: Indian Institute of Technology, Goa College of Engineering Campus, Farmagudi, Ponda-403401, Goa

*Correspondence to: list@kofo.mpg.de.

Abstract: Utilizing carbocationic intermediates in asymmetric transformations is a challenge for catalysis. While recent studies have provided promising approaches to systems proceeding through classical, trivalent carbenium ions, we were particularly intrigued by the possibility of imparting stereochemical control onto the 2-norbornyl cation, a small, fully aliphatic and positively-charged hydrocarbon that is known to adopt a non-classical structure. We now show that strong and confined imidodiphosphorimidate (IDPi) catalysts are competent acids for carrying out an asymmetric stereoablative C–C bond forming reaction, utilizing racemic exo- or endo-norbornyl derivatives to exclusively obtain the highly enantioenriched exo-product. In addition, structurally-different substrates can be converted to the same product with remarkable
enantioselectivities by leveraging the reactivity of a variety of functional groups. Mechanistic and kinetic studies suggest that all employed substrates proceed through a common cationic intermediate.

**Main Text:** The “non-classical cation controversy” (1) was a prominent chemical dispute of the 20th century and revolved around the structure of the 2-norbornyl cation, a simple bicyclic carbocation made up of seven carbon atoms. The main focus of the debate was defining whether the cation adopted a non-classical, bridged structure (1, Figure 1A) or rather existed as two rapidly equilibrating classical carbocations (2a,b, Figure 1A) (1–3). After decades of research and copious studies on the topic, X-ray crystallography unequivocally confirmed a bridged, non-classical geometry for the controversial ion (4). Beyond triggering the advancement of contemporary techniques for structural and computational analysis, the long-standing debate played a central role in the realization of carbon–carbon bond σ-donor abilities, outlining the modern bonding theory for carbocations. Namely, classical ions exist as trivalent, planar carbenium ions; whereas non-classical carbonium ions characteristically contain pentacoordinate (or higher) carbon atoms and are adequately described by a three- (or multi-) center, two-electron bond (Figure 1B). Although this dichotomy summarizes the fundamental differences between classical and non-classical ions, a continuum of possibilities lies between these two limiting cases, as a consequence of the varying degrees of charge delocalization that contribute to the stabilization of carbocationic centers through neighboring group participation (5, 6).

Carbocation chemistry has attracted great attention over the past decades and led to fundamental organic transformations and manifold industrial processes (7). However, achieving stereocontrol in reactions of carbocations still remains a formidable challenge (8, 9). Whereas classical ions have been recently, though sporadically, employed in asymmetric catalysis (10, 11), the issue of
Figure 1. The non-classical cation challenge. (A) The non-classical cation controversy. (B) Features of classical and non-classical cations and their use in asymmetric catalysis. (C) Weinsteins original experiment and the work presented herein. Bs = SO₂C₆H₄Br-p. X and Y represent a generic leaving group and nucleophile respectively.

inducing stereocontrol over carbonium ions has, to the best of our knowledge, not been addressed (Figure 1B). As for trivalent cations, the major difficulty resides in discriminating between the two faces of their planar structure (11). Nevertheless, substituents at the carbenium center can be incorporated to stabilize the vacant p-orbital and to direct the delivery of a nucleophile. In contrast, we anticipated that controlling the 2-norbornyl cation, a highly reactive, aliphatic carbocation, devoid of ancillary structural elements to serve as discriminating factors, might pose a considerable challenge. Intrigued by this opportunity, we became interested in imparting stereocontrol over the archetypal non-classical ion through asymmetric counteranion-directed catalysis (12). Indeed, we envisioned that ionic- and secondary-interactions, such as London dispersion forces, would exist in the presence of a large and confined chiral anion, and be beneficial for stereoinduction. The original experiment by Weinsteins represented the ideal starting point for our investigations (13). In his studies, he observed either complete or partial loss of optical activity during the course of acidic solvolysis of 2-exo and 2-endo-norbornyl sulfonates to furnish racemic products of exo-configuration. In an opposite fashion, we conceived an experiment in which a chiral Brönsted acid allows a diastereo- and enantioselective
Scheme 1. IDPi catalyzed enantioconvergent process from exo-norbornyl derivatives. (A) All reactions reached complete conversion of starting material 4 within the depicted reaction times. All yields are those of isolated compounds. Absolute configurations of the single enantiomers of 4 were assigned by optical rotation measurements, on the basis of literature correlations, upon cleavage of the trichloroacetimidate group. Enantiomeric ratios (e.r.) were determined by HPLC using a chiral stationary phase. The absolute configuration of 7 was determined by single-crystal X-ray diffraction. Reactions were performed with 0.1–0.2 mmol of 4 in PhMe (0.1 M) at −40 °C. The incorporation of molecular sieves (MS) was only beneficial to the yield, but exerted no effect on the enantioselectivity. (B) Two-dimensional representation and X-ray structure of IDPi catalyst 3 possessing beneficial substitutions for the achievement of optimal enantioselectivity.

reaction of racemic starting materials with a suitable nucleophile to furnish the enantiopure product (Figure 1C). Within this context, we recognized that the nature of the leaving group would be crucial in preventing undesired side- or background reactivity, e.g. the in situ liberation of an achiral Brønsted acid byproduct might enable a competing non-asymmetric transformation. Upon screening a variety of candidates, we identified trichloroacetimidate as an ideal leaving group (14), and subsequently evaluated the catalytic performance of several classes of previously reported chiral Brønsted acids in the presence of rac-4 (Scheme 1) and a wide array of
nucleophiles. Despite countless combinations being assessed, a general trend emerged for chiral phosphoric acids (15), chiral disulfonimide (DSI) (16), imidodiphosphate (IDP) (17) and iminoimidodiphosphate (iIDP) (18) catalysts, i.e. the tendency of the corresponding conjugate bases to react with the 2-norbornyl cation to irreversibly generate alkylation adducts, thus impeding catalytic turnover (19). In this regard, a distinct improvement was observed when employing our recently developed IDPi catalysts, which display superior catalytic performance due to the reduced Lewis basicity of the chiral counteranion (20). Owing to their versatile structural features, which allow for intricate fine tuning of steric and electronic properties, these catalysts demonstrate a marked ability to engage a variety of simple, aliphatic substrates in diverse chemical transformations (21). We therefore synthesized and evaluated an extensive library of IDPi catalysts in combination with an assortment of nucleophiles. The endpoint of this quest was the identification of two promising motifs capable of delivering product 7 in good yields and enantioselectivities when 1,3,5-trimethoxybenzene (6) was employed as nucleophile. Upon an exhaustive screening of conditions, we selected IDPi 3 (Scheme 1B) to carry out further investigations and found that product 7 can be obtained in very good yield (86%) and remarkable enantioselectivity (e.r. = 97:3) when the reaction between rac-4 and 6 is performed at −40 °C in toluene with a catalyst loading as low as 3 mol% (Scheme 1A, conditions a). Once we had ascertained that the racemic exo-substrate could successfully engage in an asymmetric carbon–carbon bond forming reaction, we individually submitted both enantiomers to identical reaction conditions. Congruously, (−)-4 and (+)-4 were fully converted to afford the desired product in comparable yields and identical enantiomeric ratios (Scheme 1A). We could however note a difference in the reaction rates of the two enantiomers, behavior that was also identified in a more detailed kinetic analysis (Figure 2B). In contrast, the endo-norbornyl derivative rac-5
Scheme 2. IDPi catalyzed synthesis of enantioenriched product from various substrates. Reactions were performed on 0.1–0.15 mmol scale, with concentrations ranging from 0.5 to 0.1 M. All reactions reached complete conversion of the starting material in the depicted reaction times. All reported yields are those of isolated compounds. Enantiomeric ratios (e.r.) were determined by HPLC using a chiral stationary phase.

required slightly harsher reaction conditions, only furnishing the product in ethyl acetate at room temperature with a reaction time of two hours. Nevertheless, the product was obtained in good yield and enantioselectivity (69%, e.r. = 88:12) (Scheme 2). Under the same conditions, the exo-substrate (rac-4) afforded the product within minutes in similar yield (70%) and an identical enantiomeric ratio of 88:12. These observations correlate well with Winstein’s solvolytic studies, in which the exo-precursor was found more reactive than the endo-isomer by a factor of 350 (13, 22). The noticeably higher reactivity of the exo-norbornyl ester was attributed to the anchimeric assistance offered by the C₁–C₆ bond, which is not correctly aligned in the endo-isomer to aid the ionization (23). Consistent with our approach in the exo-case, both endo-enantiomers were
independently submitted to the reaction conditions to deliver product 7 in 61–69% yield and equivalent enantiomeric ratio.

Once we demonstrated the feasibility of a diastereo- and enantioconvergent catalytic process from the 2-norbornyl trichloroacetimidate stereoisomers, we were keen to verify if this approach could be extended to other substrates that might lead to the same cationic intermediate. Therefore, we designed diverse routes to enantioenriched product 7, finding inspiration in the seminal work of Olah et al (24). We first chose to evaluate a direct protonation of norbornene (8) by means of our strong chiral Brønsted acid. Gratifyingly, the asymmetric catalytic Friedel-Crafts alkylation of 6 with norbornene (8) smoothly proceeded in toluene at 25 °C to afford 7 in 81% yield and 92:8 enantiomeric ratio (Scheme 2) (25). Encouraged by this reactivity, we furthermore embarked upon the fascinating possibility to activate hydrocarbon 9 via protonation. Indeed, under the reaction conditions used for the olefinic substrate, nortricyclene (9) could be converted to product 7 in an excellent 92% yield and equal enantioselectivity of 92:8 (Scheme 2). Notably, under identical reaction conditions, the exo-substrate (rac-4) afforded the product in a markedly shorter reaction time in good yields and with the same enantiomeric ratio (e.r. = 92:8). Next, we considered the reaction of exo-2-norbornyl fluoride (rac-10), designing an unprecedented asymmetric transformation in which a chiral silylium-based Lewis acid catalyst is used to cleave the C–F bond, while simultaneously governing the enantioselective addition of the incoming nucleophile to the resulting cationic intermediate (26, 27). As previously demonstrated, IDPi catalysts become highly active and selective “silylium” Lewis acids upon protodesilylation of a variety of silanes (21), which appoints them as ideal candidates for our experiment. Indeed, under optimized reaction conditions and in the presence of allyltrimethylsilane (11), IDPi 3
Figure 2. Mechanistic investigations. (A) Comparison of NMR spectra: 1. C2-D-labelled exo-norbornyl derivative (C2-D exo-4) (2H NMR); 2. Deuterated product mixture following the reaction of C2-D exo-4 in PhMe at 25 °C (2H NMR); 3. Product 7 (1H NMR). (B) Concentration profile of rac-4, (−)-4 and (+)-4 over time; data obtained by 1H NMR for reactions performed with 5 mol% catalyst loading in PhMe at −35 °C. (C) Relative distribution of deuterium in the product for the reactions of C2-D exo-4 at 25 °C and −40 °C, and from C2-D endo-5 at 25 °C; data obtained by 3H NMR line fitting of the individual resonances. (D) Representation of degenerate hydride shifts for the 2-norbornyl cation. Deuteride shifts are not shown, however cannot be excluded.

Catalyzes the reaction between racemic exo-2-norbornyl fluoride and 6 to furnish product 7 in 89% yield and 92:8 enantiomeric ratio (Scheme 2). Lastly, we chose to challenge our IDPi catalyst in the conversion of substrate 12 to the expected product 7. This intramolecular cyclization proceeds through the assistance of the π-electrons in the double bond (28), and requires the catalyst to coerce 12 into a bicyclic structure and additionally control the stereochemistry of the nucleophilic addition. To our delight, product 7 was successfully obtained.
in 77% yield and a satisfactory 87:13 enantiomeric ratio when the reaction was carried out in benzene at 25 °C with a moderately increased catalyst loading (Scheme 2).

The aforementioned transformations were closely investigated by NMR spectroscopy in attempt to locate and characterize ionic or covalent species, possibly composed of the norbornyl fragment and the IDPi framework. Despite gaining valuable insights into these reactions, in no case could direct evidence for the existence of such intermediates be collected. Indeed, these highly reactive, short-lived reaction intermediates are presumably undetectable under the experimental conditions, provided the sensitivity limitations of the spectroscopic method employed. To gather more information, we performed a selective deuterium labelling at C₂ for both exo-4 and endo-5 substrates and submitted these derivatives to the aforementioned reaction conditions. A subsequent analysis of the isotope position in the deuterated analogues of 7 revealed a distribution over all positions of the norbornyl unit when the exo-enantiomers were reacted at room temperature (Figure 2A). More specifically, the probability to locate the deuterium isotope was predominant at C₁, C₂ and C₆, while the remaining positions were involved to a minor extent (Figure 2C, orange). Interestingly, the profile obtained from the reaction of the endo-substrate was remarkably similar (Figure 2C, fuchsia). Lowering the reaction temperature of deuterated exo-4 distinctly hampered the internal rearrangements responsible for locating the isotope over the peripheral positions of the norbornyl fragment, while the incidence at C₁, C₂ and C₆ remained nearly unaffected (Figure 2C, turquoise). These results point to the existence of a carbocationic intermediate that, in analogy to earlier studies for the non-classical 2-norbornyl cation, undergoes fast 6,1,2- and slower 3,2-hydride shifts (29, 30) (Figure 2D). Moreover, the consistent isotope distributions and the enantioselective outcomes suggest the participation of a common intermediate in the reaction of all substrates employed.
In view of these results, we believe to have made a crucial contribution to the fascinating history of the 2-norbornyl cation, with a modern take on Winstein’s original experiment and Olah’s pioneering work. Furthermore, IDPi catalysts demonstrated potential for the non-trivial activation of C–C π- and σ-bonds, as well as C–F bonds, while concurrently engaging them in enantioselective transformations. Additionally, we showed that IDPi catalysts are competent Brønsted and Lewis acids in exerting enantiocontrol over simple and highly reactive carbocations, paving the way for the development of further transformations that involve intermediates structurally prone to non-classical interactions.
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References and Notes:


