Kinetic Resolution of Allyltriﬂamides through a Pd-Catalyzed C–H Functionalization with Allenes: Asymmetric Assembly of Tetrahydropyridines

José Manuel González, Borja Cendón, José Luis Mascareñas, and Moisés Gulías*

ABSTRACT: Enantioenriched, six-membered azacycles are essential structural motifs in many products of pharmaceutical or agrochemical interest. Here we report a simple and practical method for enantioselective assembly of tetrahydropyridines, which is paired to a kinetic resolution of α-branched allyltriﬂamides. The reaction consists of a formal (4+2) cycloaddition between the allylamine derivatives and allenes and is initiated by a palladium(II)-catalyzed C–H activation process. Both the chiral allylamide precursors and the tetrahydropyridine adducts were successfully obtained in high yields, with excellent enantioselectivity (up to 99% ee) and selectivity values of up to 127.

The assembly of chiral products through the enantioselective functionalization of C–H bonds represents one of the more relevant challenges in modern organic synthesis.1,2 In recent years, a series of brilliant strategies to carry out this type of reactions using transition metal catalysis, and relying on the presence of directing groups, have been described. One of the most relevant approaches to generate asymmetry consists of the desymmetrization of prochiral C–H bonds using palladium catalysts and monoprotected amino acids as metal ligands, a strategy that was pioneered by the group of Yu.3 Inspired by this research, we have recently published a palladium-catalyzed desymmetrization of diarylmethanamine triﬂamides by reaction with allenes to form chiral tetrahydroisoquinolines.3e Although these methodologies are appealing, they require the presence of symmetric groups in the molecule, which represents a significant restriction in terms of the structural variability that can be achieved. Furthermore, the limitation to aromatic substrates reduces possibilities for subsequent synthetic manipulations.

Alternatively, enantioselective reactions can also be performed using kinetic resolutions (KRs). These strategies present the intrinsic limitation of yield, but they enable the recovery of the precursors in an enantioselective manner and are very attractive in terms of scope.4 In this context, the group of Yu has recently reported a palladium-catalyzed kinetic resolution of α-branched benzyl amine derivatives via C–H iodonation or cross-coupling reactions.5a,b They also reported the kinetic resolution of racemic allyltriﬂamides via cross-coupling reactions with boronates (Scheme 1A).5c Remarkably, related asymmetric reactions using allylamines, or involving the activation of any type of alkenyl C–H bond, have never been described. This scarcity might be associated with the notion that the allenes could engage in secondary reactions or the perception that attaining effective chiral discrimination might be especially challenging in comparison with reactions involving aromatic Csp2–H bonds (Scheme 1B).

Scheme 1. Kinetic Resolution of α-Branched Amines

A. Previous work: kinetic resolution of racemic benzyl and alkyl amines

B. This work: kinetic resolution of allyl amines via C–H functionalization with allenes

C. Challenges of the allylamine C–H functionalization

D. Natural products with a six-membered azaheterocycle core

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Herein we report the discovery of a practical and efficient methodology for the kinetic resolution of α-branched allyltrimidamides based on a Pd-catalyzed C−H activation process (Scheme 1B). Very importantly, this resolution is performed using highly substituted alkenes, which are traditionally difficult substrates for C−H functionalization reactions. Furthermore, the activation is coupled to a formal cycloaddition rather than to a simple C−H functionalization, therefore allowing a rapid increase in structural complexity, in addition rather than to a simple C−H functionalization, thereby allowing a rapid increase in structural complexity, in addition rather than to a simple C−H functionalization, thereby allowing a rapid increase in structural complexity, in addition rather than to a simple C−H functionalization, thereby allowing a rapid increase in structural complexity, in addition rather than to a simple C−H functionalization, thereby allowing a rapid increase in structural complexity.

Needless to say, tetrahydropyridine and related piperidine derivatives are very interesting products owing to the elaboration possibilities offered by the presence of double bonds.

Table 1. Optimization of Conditions

| Entry | Deviation from above conditions | C% (%) | α (%) | ρ (%) |
|-------|-------------------------------|--------|-------|-------|
| 1     | none                          | 49     | 94    | 100   |
| 2     | Boc-Val-NHOMe                 | 45     | 82    | 66    | 20    |
| 3     | Boc-Leu-NHOMe                 | 37     | 88    | 52    | 26    |
| 4     | Boc-Phe-OH                    | 63     | 58    | 99    | 18    |
| 5     | Boc-Val-OH                    | 59     | 58    | 84    | 10    |
| 6     | Boc-Leu-OH                    | 64     | 54    | 98    | 14    |
| 7     | Boc-t-Leu-OH                  | 58     | 50    | 70    | 6     |
| 8     | Boc-Ile-OH                    | 65     | 50    | 92    | 9     |
| 9     | TcBoc-Phe-OH                  | 64     | 20    | 36    | 2     |
| 10    | Ac-Phe-OH                     | 31     | 48    | 22    | 4     |
| 11    | 2,6-F-F-Bz-Phe-OH             | 47     | 60    | 56    | 7     |
| 12    | 0.5 equiv Cu(OAc)2·H2O        | 36     | 94    | 52    | 54    |
| 13    | AgNO3 as oxidant              | 9      | 86    | 8     | 14    |
| 14    | Ag2CO3 as oxidant             | 6      | 92    | 6     | 25    |
| 15    | THF as solvent                | 25     | 84    | 2     | 15    |
| 16    | DCE as solvent                | 39     | 86    | 56    | 23    |
| 17    | i-PrOH as solvent             | 51     | 78    | 80    | 20    |
| 18    | i-AmylOH as solvent           | 55     | 80    | 99    | 40    |
| 19    | no base                       | 4      | 44    | 2     | 3     |
| 20    | no DMSO                       | 12     | 72    | 10    | 7     |

aConditions: rac-1a (0.1 mmol), 2a (0.1 mmol), Pd(OAc)2 (10 mol %), ligand (40 mol %), Cu(OAc)2·H2O (2 equiv), Cs2CO3 (1.5 equiv), DMSO (15 equiv), PhCH3 (1.2 mL), air, 70 °C, 24 h.

bCalculated conversion, C = εmax/(εmax + εpr).

cEnantiomeric excess (ee) was determined by chiral HPLC analysis of the reaction crude.

dSelectivity (s) = ln[(1 − C)/(1 − εmax)]/ln[(1 − C)/(1 + εmax)].

DMSO (10:1), in the presence of 10 mol% of palladium acetate, 2 equiv of copper acetate, 1.5 equiv of cesium carbonate, and 40 mol% Boc-1-Phe-NHOMe, provides the desired cycloadduct 3aa with an excellent 94% ee (94% conversion after 24 h) (Table 1, entry 1). The remaining starting material was isolated with a 90% ee. Decreasing the amount of ligand favors the conversion rate but affects the enantioselectivity of the product. Not surprisingly, when Boc-1-Phe-NHOMe was used as ligand, the opposite enantiomers were obtained with the same enantioselectivity. Changing the ligand to other diprotected (entries 2 and 3) or monoprotected amino acids (entries 4−8) resulted in lower conversions and poorer ee’s. It should be noted that, although the use of Boc-phenylalanine as ligand led to a moderate enantioselectivity (58% ee), it made possible to recover the starting amide with 99% enantioselectivity (entry 4). Indeed, this ligand gave also good results for some of the other substrates tested (see below, Scheme 3). Significant decreases in conversion and enantioselectivity were observed when the tert-butyloxy carbonyl protecting group of the amino acid was replaced by an acetyl, trichloro-tert-butyloxy carbonyl, or difluorobenzoyl group (entries 9−11). Moreover, we found that, when using less copper acetate, or replacing it with other
oxidants, such as silver acetate or silver carbonate, the conversions and enantioselectivities were poorer (entries 12−14). The use of solvents other than toluene, such as THF, DCE, or isopropanol, clearly gave worse results in both conversion and selectivity (entries 15−17), while with tert-amyl alcohol we obtained an ee of 80% for the product and an excellent 99% ee for the recovered starting material (entry 18).

We also found that, without base or DMSO, the reaction hardly progresses (entries 19 and 20), and the enantioselectivity is greatly diminished.

The scope of the reaction with respect to the allene component was studied using the above optimized conditions, albeit with small adjustments in temperature, and the results are summarized in Scheme 2. Therefore, when the allyltriflimide was tested with a different 1,1-disubstituted allene (5-vinylidenonane), it resulted in the formation of the
cycloadduct 3ba with a 90% ee, while the starting amide was recovered with 82% ee (selectivity factor of 48).

The reaction also works very nicely with monosubstituted allenes such as commercially available propa-1,2-dien-1-ylcyclohexane (2c), the silyl-protected buta-2,3-dien-1-ol 2d, or allenes containing acetate (2f) and phthalimide (2e) functional groups, leading to enantioselectivities up to 94% in the products and over 96% in the corresponding starting materials. In contrast, buta-2,3-dien-1-ol failed to participate in the annulation, and the reaction provided a complex mixture of products. In the case of allenes with aromatic substituents (2g and 2h), we observed very good enantiomeric excess in the products (up to 94% ee) but more modest enantioselectivities.
for the starting materials (62–78% ee). Remarkably, trisubstituted allenes (2i) can also work with only a slight erosion of the enantioselectivity of the product (86% ee). In this reaction we also observed the formation of a small proportion of a different regioisomer.

 Gratifyingly, in most of the cases the products were formed with high E,Z diastereoselectivity. The preferred formation of the Z-isomer with monosubstituted allenes is likely a consequence of steric effects associated to the interaction of the phenyl group of the alkene with the substituent of the allene.

The optimized conditions were also used for further evaluating the scope of the reaction with regard to the allytrimlamide precursors. Pleasingly, we found that allylamine derivatives with other groups at the α-position, including methyl, butyl, and isobutyl, are well tolerated. In all cases the reactions took place with good yields and excellent enantioselectivities (Scheme 3, 1b−1d, up to 94% ee for products and starting materials). The crystallization of compounds 3ba and 1b allowed determination of the absolute configuration R and S, respectively, through X-ray crystallographic analysis (Scheme 3, top right). [Their crystal structure data are deposited to the CCDC.]

We also analyzed the reactivity of the precursors with other substituents at the terminal and internal positions of the alkene moiety. As illustrated with the formation of products 3ea−3ia and enantioenriched precursors 1e−1i, enantioselectivities up to 96% and almost enantiopure allylsulphonamides were obtained (selectivities up to 127). Even reactants with the alkene embedded in a cyclohexyl ring, such as 1h and 1i, were effective substrates, generating chiral bicyclic structures. Substrates bearing terminal alkienes (1j and 1k) also led to good results, although in this case with slightly lower conversions and enantioselectivities, perhaps because there is less steric encumbrance (3ja and 3ka, up to 90% ee). Remarkably, homoallyl amide substrates like 1l and 1m, in which the chiral center is in the β-position relative to the amine, also participated in the cycloaddition. In this case, as for the formation of 3ka, N-Boc-phenylalanine was a more suitable ligand. Of course, different allylsulphonamides can be combined with different allenes, and therefore a great variety of products can be formed with similar levels of enantioselectivity (see, for instance, 3lc, with 90% ee). As can be deduced from the reaction conditions (Scheme 3), the optimal temperature depends on the type of precursors, likely because of steric factors.

The presence of unsaturations in the cyclic products provides for performing divergent manipulations. For instance, treatment of 3ac with hydrogen gas in the presence of palladium over carbon led to product 4 in an excellent 91% yield (Scheme 4). Therefore, the hydrogenation is accompanied by an isomerization process which makes it possible to create a new stereocenter in a fully diastereoselective manner. The product 3ac can also react selectively with ruthenium trichloride to give, in 66% yield, the tetrahydropropyridine 5, exhibiting an α,β-unsaturated motif. Importantly, the trityl group of the amide can be successfully removed using Red-Al in quantitative yield. In all cases the enantio purity of the product was intact.

As commented before, one of the advantages of this type of kinetic resolution strategies is that the recovered precursor might also be an invaluable platform to produce different types of enantioenriched derivatives. In our case, the chiral allytrimlamides can be easily manipulated owing to the presence of the double bond. For example, compound (S)-1a (99% ee) can be converted into the chiral keto amino product 7 under oxidative conditions (Scheme 5). Amine (S)-1a can be also alkylated with propargyl bromide, and the resulting enyne can be cyclized to the interesting piperidine 9 using iridium catalysis. This optically active product (99% ee), obtained as a single diastereoisomer, exhibits up to four stereocenters. Finally, we also demonstrated that enantioenriched compounds like (S)-1a can participate in the (4+2) annihilation reaction with allene 2a under standard conditions, using the D-amino acid ligand derivative, to give the corresponding enantiomer (S)-3aa (88% yield), which exhibit the same enantiomeric excess as the starting material.

Overall, we have discovered a new enantioselective annihilation process based on a Pd(II)-catalyzed reaction of allylamine derivatives and allenes and relying on an asymmetric C–H activation step. The reaction allows very efficient kinetic resolutions and provides an unprecedented access to a broad range of enantioenriched piperidines and highly substituted allyl amines. These enantioenriched products can be easily converted into several appealing azacycles and different nitrogenated derivatives. The methodology provides a powerful atom- and step economical approach to this type of optically active products.

ASSOCIATED CONTENT

+ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c01929.

Experimental details and characterization data for all new compounds (PDF)

Accession Codes

CCDC 2043705 and 2043710 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

Moisés Gulias – Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS) and Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain; orcid.org/0000-0001-8093-2454; Email: moises.gulias@usc.es

Authors

José Manuel González – Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS) and Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain

Borja Cendón – Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS) and Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain

José Luis Mascareñas – Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS) and
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