Organic Letters 21.11 (2019): 4345-4349

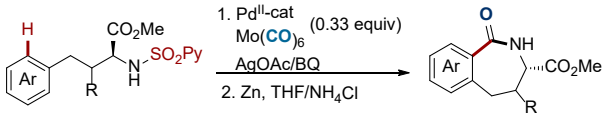
DOI: https://doi.org/10.1021/acs.orglett.9b01523

Access to Benzazepinones by Pd-Catalyzed Remote C–H Carbonylation of γ-Arylpropylamine Derivatives

Mario Martínez-Mingo[a], Nuria Rodríguez,*[a,b] Ramón Gómez Arrayás,*[a,b] and Juan C. Carretero*[a,b]

[a]Departamento de Química Orgánica, Facultad de Ciencias. Universidad Autónoma de Madrid (UAM), Cantoblanco, 28049 Madrid (Spain). [b] Institute for Advanced Research in Chemical Sciences (IAdChem), UAM, Cantoblanco, 28049 Madrid.

Supporting Information Placeholder



ABSTRACT: The first general method for the construction of seven-membered rings through Pd-catalyzed C(sp^2)–H carbonylation at remote ε-position of γ-arylpropylamine derivatives, including chiral α-amino acids, has been developed using $Mo(CO)_6$ as CO source, furnishing richly functionalized benzo[*c*]azepine-1-one derivatives. The readily removable *N*-SO_2Py protecting/directing group provided high levels of chemo-, regio- and diastereoselectivity. Furthermore, this method is amenable to the post-synthetic modification of complex molecules such as small peptides.

The benzazepine skeleton is a privileged scaffold in terms of biological activity[1] (Figure 1). However, access to structural diversity around this scaffold is limited by the availability of general methods for their synthesis, since classical approaches largely rely on multi-step strategies.[2] The asymmetric synthesis of benzazepines is even more underexplored.[3]

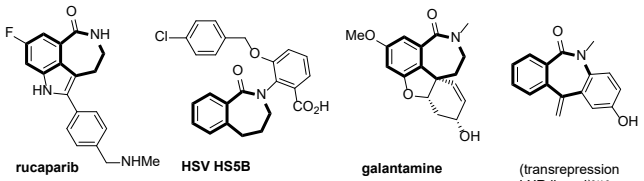


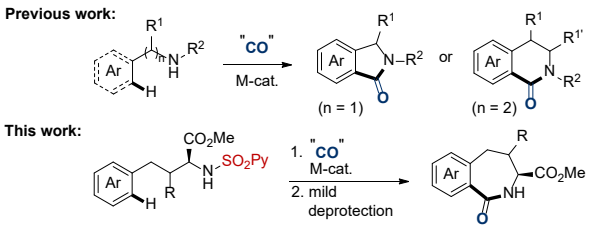
Figure 1. Bioactive Molecules Based on a 2-Benzazepinone Core

Given the significant advances in the arsenal of C–H functionalization strategies concerning the construction of five- and six-membered heterocyclic ring systems,[4] it is surprising that only a handful of protocols have been reported enabling the assembly of seven-membered rings.[5-10] Most of them rely on [4+3] annulation of benzyl- or phenethylamine derivatives at various oxidation levels with unsaturated systems.[5] A Pd^{II}-catalyzed [3+2+2]-type oxidative annulation of isatins with alkynes has appeared for accessing azepines,[6] whereas the assembly of axially chiral dibenzazepinones has been recently achieved via Pd^0-catalyzed C–H intramolecular arylation.[7] Some rare examples for azepine synthesis via intramolecular oxidative C–H coupling[8] and C–H amidation[9] have also been reported. Despite these advances, novel C–H functionalization approaches would be of substantial utility.

While the C–H carbonylation of amines is a powerful method for 5- and 6- membered ring benzolactam synthesis (Scheme 1),[11,12] there is no catalytic method for the assembly of benzazepinones.[13] This lack of precedents likely stems from the difficulty in forming metalacycles larger than usual five- or six-membered rings.[13]

During our studies on Pd-catalyzed γ-C(sp^3)–H carbonylative cyclization of aliphatic amines leading to γ-lactams,[14] we observed that the *N*-SO_2Py directing group enabled a remote ε-C(sp^2)–H carbonylation to the corresponding benzazepinones, yet the reaction was heavily dependent on the substitution and showed modest reactivity. While these results provide a powerful proof of concept, this elusive chemistry is far from being solved. Herein we describe the development of a practical and general method for the assembly of the benzazepinone skeleton from γ-arylpropylamines and the study of its synthetic potential.

Scheme 1. C–H Carbonylation Strategies to Benzolactams

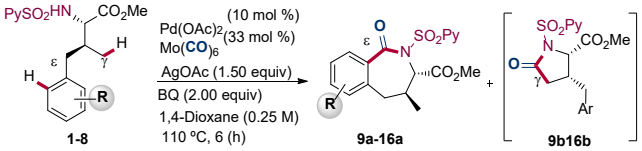


At the outset, we chose the γ-*p*-tolyl-substituted L-valine derivative **1**[15] to study the carbonylative annulation because it would test the chemoselectivity of the catalyst toward the ε-C(sp^2)–H bond (to form the benzazepinone **9a**) versus the γ-C(sp^3)–H bond (leading to the γ-lactam **9b**, Table 1). Following

some optimization (see SI for full studies), we were pleased to observe clean carbonylation of **1** with $Mo(CO)_6$ (0.33 equiv)[16] using $Pd(OAc)_2$ (10 mol%), in combination with AgOAc (1.5 equiv) and 1,4-benzoquinone (BQ, 2.0 equiv) in 1,4-dioxane after 6 h at 110 ºC. Under these conditions, benzazepinone **9a** was obtained as the only product in 80% isolated yield (entry 1). Control experiments indicated that all the reaction parameters are essential to attain significant catalytic activity (see SI).

The examination of the electronic effects of the aryl substituents on the chemoselectivity revealed a profound impact on the reaction outcome. Notably, the desired benzazepinone was the main product, although a complete ε-C(sp^2)–H selectivity was observed only in the derivatives holding electron-releasing substituents at *para*- or *meta*-position (**9a**, **10a** and **15a**, 70-80%).

Table 1. ε-C(sp^2)–H vs γ-C(sp^3)–H Chemoselectivity[a]



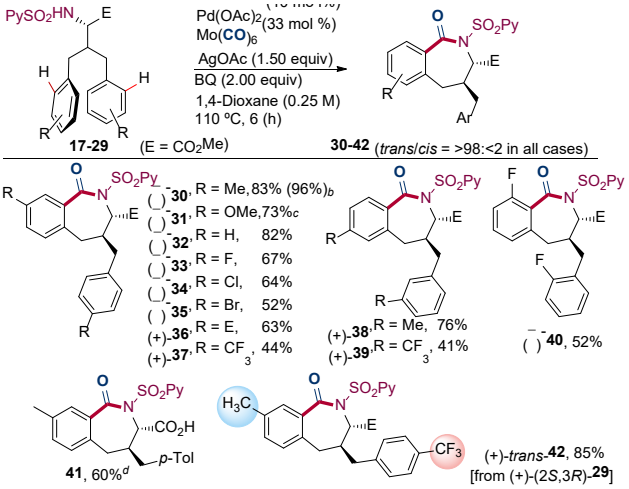
entry[a]	R (substrate)	product	**a** (%)[b]	**b**(%)[b]
1	4-Me (**1**)	**9**	80	–
2	4-OMe (**2**)	**10**	70	–
3	H (**3**)	**11**	57	27
4	4-Cl (**4**)	**12**	50[c]	21
5	4-Br (**5**)	**13**	46	28
6	4-(CO_2Me) (**6**)	**14**	49	23
7	3-Me (**7**)	**15**	72	–
8	2-Me (**8**)	**16**	35[c]	16

[a] Conditions: substrate (0.10 mmol), $Pd(OAc)_2$ (10 mol %), $Mo(CO)_6$ (0.033 mmol), AgOAc (1.50 equiv), BQ (2.00 equiv), dioxane, 110 ºC,6 h, Ar. [b] Isolated yields. [c] After *N*-deprotection.

Electron-poor groups led to modest chemoselectivity, delivering mixtures of both benzazepinone and γ-lactam products. When a *meta*-substituent is present, the reaction occurred at the more sterically accessible *ortho*-position with complete regiocontrol (**15a** entry 7). An *ortho*-subsituent is tolerated (**16a**, entry 8), though it also serves to oppose the ε-C(sp^2)–H selectivity. Nevertheless, in all cases useful yields of benzazepinone products were attained after chromatographic separation. It is important to note that Cl and Br groups remained intact (entries 4 and 5).

We next examined γ,γ′-diaryl-L-valine derivatives,[15] having two diastereotopic benzyl groups (Scheme 2). Interestingly, excellent *trans*-diastereoselectivity (>98:2) was observed in all cases, which likely arises from formation of the more stable *trans*-palladacycle. Wide functional tolerance and heightened reactivity endowed by electron-rich groups was maintained. No appreciable racemization took place from enantioenriched substrates, as demonstrated in substrate **30** (83%, 98% *ee*). A free COOH group was also tolerated (**41**, 60% conversion). Moreover, the reaction can be scaled up to 1 mmol scale with even better results (product (–)-**30**, 96%), thus emphasizing the robustness of this method.

Scheme 2. Reaction of γ,γ-Diarylated Valine Derivatives[a]

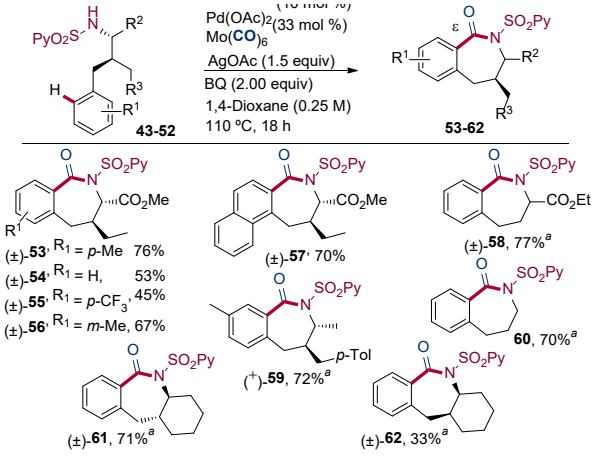


[a] Conditions identical as those shown in Table 1. [b] Isolated yield when reaction is scaled-up to 1.00 mmol scale scale. [c] 98% ee (determined by HPLC using chiral stationary phase). [d] Conversion yield (determined by ^{1}H NMR).

The inherent preference for electron-rich aromatics and *trans*-diastereoselectivity allows for achieving selectivity in substrates with two distinct γ-aryl groups. Thus, (2*S*,3*R*)-**29** with a matched combination of these two requirements led to *trans*-**42** in 85% yield with complete chemo- and stereoselectivity, whereas the mismatched (2*S*,3*S*)-**29** provided a mixture of *trans*+*cis* products (not shown, see SI).

The present system could also be extended to γ-arylated amino acid derivatives different from valine esters such as the (±)-*allo*-isoleucine derivatives (Scheme 3, **53-58**, 45-77%). The ethyl (*S*)-2-amino-4-phenylbutanoate, lacking ramification at the β-carbon, provided the corresponding benzazepinone **58** in 77% yield (25 mol% of Pd-catalyst).

Scheme 3. Extension to Amino Acid Derivatives Different from Valine Ester and Simple Aliphatic Amines



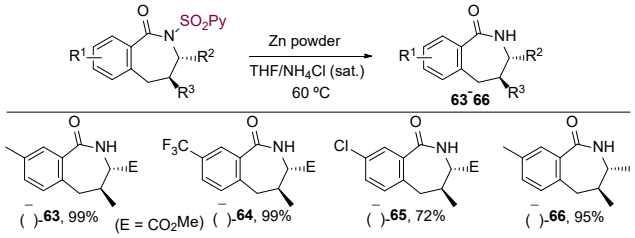
[a] $Pd(OAc)_2$ (25 mol%), AgOAc (2 equiv) and BQ (3 equiv).

Simple aliphatic amine derivatives were also amenable to the reaction, but with lessened reactivity, requiring higher loading of Pd (25 mol%) and oxidant to achieve useful yields (Scheme 3, **59-62**). Compatibility with a more flexible substrate lacking branching at both α- and β-positions was striking (**60**, 70%) since this constraint is often necessary as turning element for maximizing the reactive conformation. The construction of tricyclic skeletons from cyclohexanamine derivatives is also illustrated, with the *trans*-derivative showing higher reactivity

(**61**, 71%), than the *cis*-one (**62**, 33%).[17] Overall, the scope highlights the validity of the method to construct efficiently benzazepinones with varied substitution patterns.

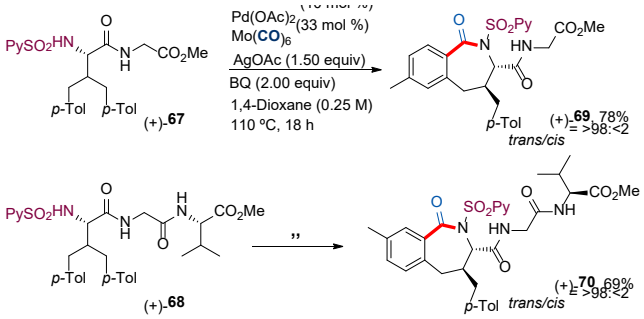
The reductive removal of the *N*-SO_2Py group[18] occurs readily under mild conditions (Zn, THF/sat.NH_4Cl), furnishing the corresponding free lactams in good yields with full preservation of the stereochemical integrity and high chemoselectivity (Scheme 4).

Scheme 4. Removal of the *N*-SO_2Py Protecting Group



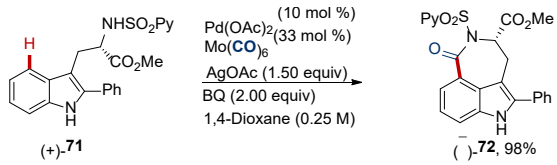
The increased complexity of small peptides represents a demanding test for the late-stage funcionalization capability of this method.[19] We were delighted to find that the reaction of both valine-glycine dipeptide **67** and valine-glycine-valine tripeptide **68** derivatives took place efficiently, providing the corresponding modified peptides **69** and **70** in 78% and 69% yield, respectively (Scheme 5). Again, the reaction occurred with very high *trans*-diastereoselectivity (*trans*/*cis* = >20:<1).

Scheme 5. Late-Stage Modification of Di- and Tripeptides



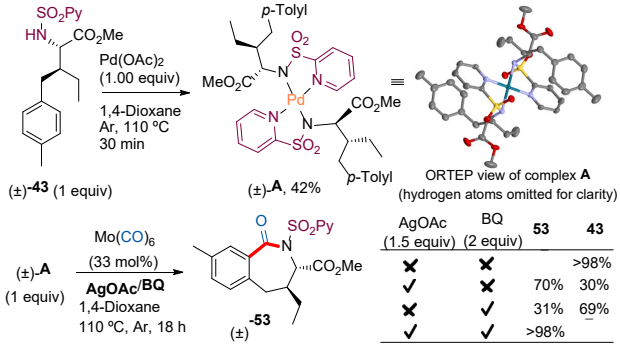
This method also enabled the construction of the tricyclic skeleton of a chiral analogue of rucaparib, a recently approved drug for ovarian cancer (Figure 1).[1c] Thus, simple exposure of the *N*-SO_2Py-protected (*S*)-tryptophan methyl ester **71** to the standard carbonylation provided the azepino-indolone **72** in 98% yield (Scheme 6). Previous routes to rucaparib rely on lactamization of a prefunctionalized 4-carboxylate indole system.[1c,20]

Scheme 6. Synthesis of a Chiral Analogue of Rucaparib



To gain preliminary mechanistic data, the reactivity of complex **A**, prepared from (±)-**43**, was examined (Scheme 7, see SI for details). X-ray structure of complex **A**[21] showed two units of **43** coordinated to Pd as mono-anionic bidentate *N*,*N*-ligands, thus highlighting the bidentate role of the *N*-SO_2Py group. Either BQ or AgOAc was crucial for the complex **A** to undergo cyclization. The absence of an external base in the mixture suggests that one unit of **43** may function as inner-sphere base needed for the C–H bond cleavage. Complex **A** proved to be a competent catalyst precursor (10 mol%) for the conversion of **43** into **53** (75% yield, see SI).

Scheme 7. Stoichiometric Experiments



An analysis by ESI-HRMS of the crude reaction of complex **A** with $Mo(CO)_6$ (0.33 equiv) and BQ (2.00 equiv) in dioxane upon 15 min showed a dominant molecular ion peak at *m/z* $(2M+Na)^+$: 827.2397 attributable to product **53** (Figure 2). Interestingly, two peaks could be assigned to Pd-complexes. The peak at *m/z* $(M+H)^+$: 857.1885 corresponds to complex **A** (calculated *m/z* $(M+H)^+$: 857.1870), while the minor peak **B** at *m/z* $(M+H)^+$: = 481.0417 matches with the seven membered palladacycle presumably formed upon ε-C(sp^2)-H activation (calculated *m/z* $(M+H)^+$ = 481.0413).

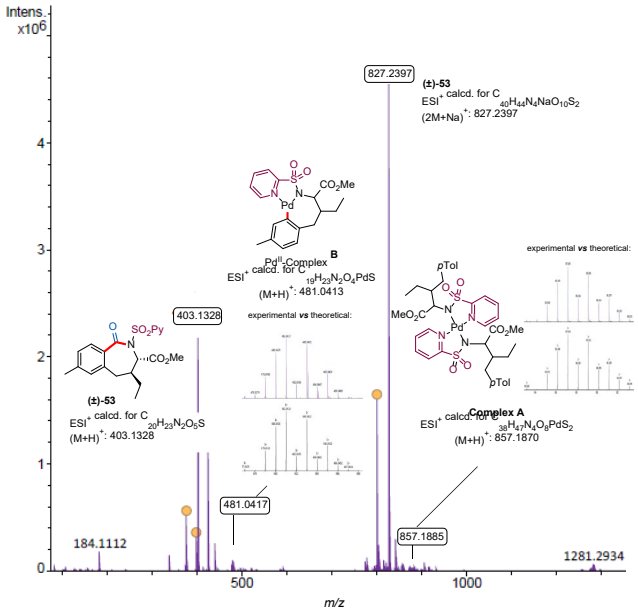


Figure 2. Key Area of the ESI-HRMS Spectrum of the Crude Reaction Mixture of Complex **A** after 15 min

Monitoring the reaction of **43** into **53** with 1 equiv of $Pd(OAc)_2$, $Mo(CO)_6$ (0.33 equiv) and BQ (2 equiv) at 55 °C with d_8-THF revealed fast and clean formation of complex **A**, which reached its highest concentration after 2 h before it is slowly consumed at the expense of product formation (Figure 3). Increasing formation of AcOH was observed since very early stages of reaction. From these results, it appears that complex **A** is acting as the resting state of the Pd catalyst.

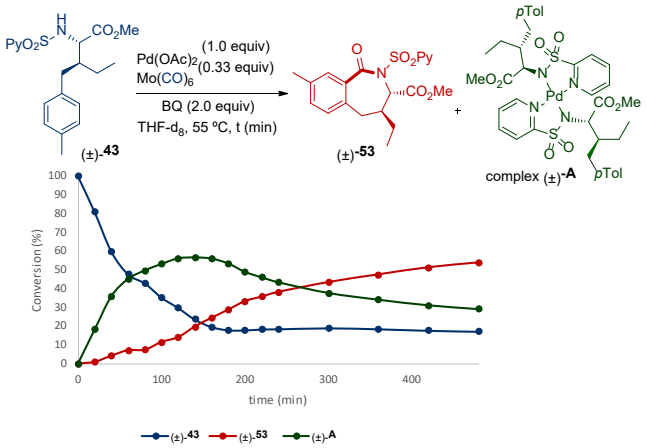
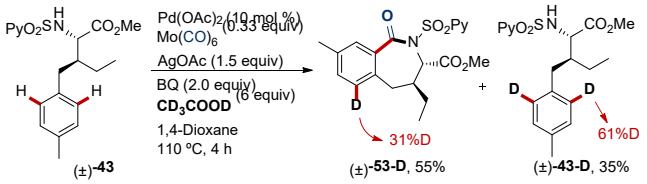


Figure 3. Carbonylative Cyclization of **43** under Stoichiometric Pd Monitored by ^{1}H NMR (THF-d_8).

The carbonylation of **43**, conducted in the presence of d_4-acetic acid (6 equiv) under otherwise standard conditions and stopped at low conversion, resulted in deuterium incorporation at the *ortho*-position of both the product (**53-D**, 55% yield, 31% D) and the recovered starting material **43-D** (35% yield, 61% D) (Scheme 8). This may arise from a fast and reversible metalation/proto(deutero)demetalation step prior to CO insertion. On the other hand, the strong preference for electron-rich arenes suggests a partial electrophilic palladation character for the C–H cleavage mechanism, which is consistent with literature concerning remote C(sp^2)–H functionalization.[22]

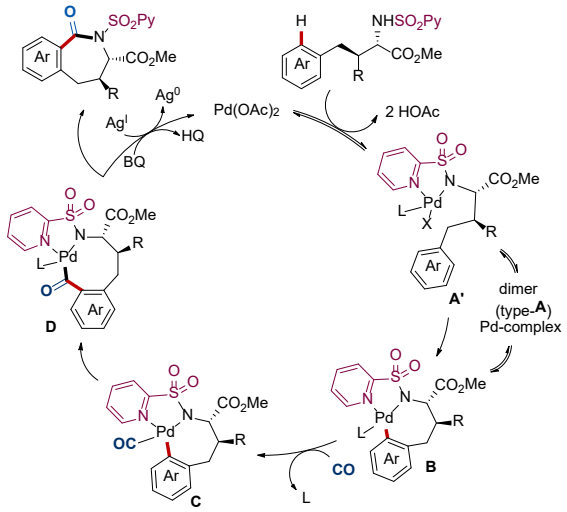
Scheme 8. Deuterium-labeling experiment



A simplified catalytic cycle is presented in Scheme 9. Initial substrate coordination to $Pd(OAc)_2$ would generate complex **A'**, in equilibrium with complex **A** (reversible off-cicle reservoir). Then, Pd^{II}-catalyzed C–H activation of **A'**, would lead to complex **B** which would undergo coordination to CO (**C**) followed by carbonyl insertion across the Pd–C bond to afford complex **D**. Reductive elimination would release the benzazepinone product, along with reduced Pd^0 species that would then reoxidize back to the active Pd^{II} species *via* the combined action of BQ and AgOAc.

In conclusion, the method described here provides a significant advancement to catalytic C–H carbonylation of amines as it enables unprecedented general access to the seven-membered ring of benzazepinones. The excellent directing ability of the *N*-SO_2Py group under Pd-catalysis, along with its easy removal under very mild conditions are key points of this protocol. The capability of this method for late stage modification and heterocycle functionalization highlight its potential to find applications in targeted synthesis.

Scheme 9. Plausible Catalytic Cycle



ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures and spectral data for all new compounds.
Single-crystal X-ray diffraction data for complex **A** (PDF)

AUTHOR INFORMATION

Corresponding Author

*e-mail for N.R.: n.rodriguez@uam.es
*e-mail for R.G.A.: ramon.gomez@uam.es
*e-mail for J.C.C.: juancarlos.carretero@uam.es.

ORCID

Nuria Rodríguez: 0000-0002-7174-4555
Ramón Gómez Arrayás: 0000-0002-5665-0905
Juan Carlos Carretero: 0000-0003-4822-5447

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank the Spanish Ministerio de Economía y Competitividad (Project CTQ2015-66954-P, MINECO/FEDER, UE) for financial support. M.M.-M. thanks MINECO for a FPI predoctoral fellowship. N.R. thanks the European Commission for a Marie Curie Career Integration Grant (CIG: CHAAS-304085). Prof. Inés Alonso (Departamento de Química Orgánica, UAM) is gratefully acknowledged for helpful discussions.

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