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Palladium-Catalyzed Domino Cycloisomerization/Double Condensation of Acetylenic Acids with Dinucleophiles

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Abstract: Metal-catalyzed cascade processes based on hydrofunctionalization of alkynes are receiving much more attention because of their potential to provide advantageous approaches to otherwise synthetically challenging compounds. An alternative catalyst system has been found for the domino cycloisomerization/cyclocondensation reaction involving acetylenic acids and heterodinucleophiles. A CNN pincer palladium(II) complex, acting as a homogeneous catalyst, provides the corresponding polyheterocycles with a higher substrate/catalyst ratio. Other palladium sources were also tested and discarded, and a number of mechanistic studies including poisoning assays, kinetic plots, TEM images, XRD spectra and UPLC-MS analysis of reaction intermediates were conducted in order to shed light on the role of this pincer catalyst and the catalytic cycle involved in the cascade reaction. As a result, a more nuanced mechanism is tentatively proposed.

Keywords: palladium; domino reactions; alkynes

1. Introduction

Metal-catalyzed cascade reactions have attracted much more attention as an expeditious access to relatively complex frameworks from readily available substrates. In this regard, the construction of cyclic or polycyclic structures by means of cascade processes involving alkynes is a rapidly emerging field on account of the increasing number of reports on this topic [1–4]. A particularly appealing cascade reaction between alkynoic acids and dinucleophiles was discovered due to the elegant works by Dixon [5–7], Patil [8,9], Liu-Zhao [10–17], Reddy [18,19] and Lei [20]. Au(I) (often Au(I)-Ag(I)), Cu(II), and recently, Ru(II) catalysts were the key for this transformation leading to a number of polyheterocycles, including structural analogues of quinazoline alkaloids Tryptanthrine, Batracycin, Peganine, Vasicinone, or Mackinazoline, and the inhibitor of aldo-keto reductase AKR1C3 depicted in Figure 1 [21,22]. In most cases, a plausible reaction mechanism has been proposed, suggesting an initial cycloisomerization of the alkynoic acid followed by a nucleophilic attack at the corresponding enol lactone intermediate to form a ketonamide that under acidic (Brönsted or Lewis) conditions leads to the cyclized product via an acyliminium ion intermediate (Scheme 1). A minimum amount of 0.5 mol% of metal catalyst is required to affect the cascade process (catalyst loading ranging from 0.5 to 20 mol%) [5–19].

Following our research on metal-catalyzed transformations involving alkynes [23], we had described an unprecedented amount of activity for the cycloisomerization of alkynoic acids exhibited by a palladium NNC complex (1) [24]. On this basis, we envisaged that such a more active catalyst could also promote a domino process leading to polycyclic structures if reacted with suitable dinucleophiles. In addition to a new metal participating in this reaction, this approach could lead to a substantial enhancement in the catalytic efficiency, which is increasingly becoming a priority in sustainable chemistry [25–27]. In this regard, we wish to present an exceedingly active catalyst system for the cascade
reaction between alkynoic acids and N,O- and N,N-dinucleophiles as well as an insight into the reaction mechanism.

![Figure 1. Structure of quinazoline alkaloids and reductase inhibitor pyrrolobenzimidazolone.](image)

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![Scheme 1. Postulated catalytic cycle and reported metal catalysts for the cascade reaction between alkynoic acids and dinucleophiles.](image)

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## 2. Results and Discussion

Pentynoic acid 2a and anthranilic acid 3a were chosen as model substrates for a number of initial assays. Different palladium sources (Pd(OAc)$_2$, PdCl$_2$, and Pd(PPh$_3$)$_2$) were tested, and the results compared to those obtained from NNC palladium complex 1. The catalyst loading was set at $10^{-2}$ mol% in order to meet the aforementioned requirements of efficiency. The amounts of base and/or additive were also minimized following the same criteria. After a number of initial experiments, it became clear that the process required chloroform as a solvent and triethylamine as a base to get reasonable yields, as negligible results were obtained from other bases (KOH, NaOH, LiOH, KO$_2$Bu, K$_2$CO$_3$, Cs$_2$CO$_3$, DBU, DIPEA, pyridine and DMAP) and solvents (THF, PhMe, MeOH, CH$_2$Cl$_2$, DMF, DMA, DMSO and MeCN) (see Supplementary Material for further details).

Only pincer complex 1 provided target benzopyrrolo[1,3]oxazine-1,5-dione 4a even using triethylamine in chloroform (Figure 2, entries 1–4), and the presence of a Lewis acid additive proved beneficial for the reaction outcome (entries 5–9).
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Only pincer complex 1 provided target benzopyrrolo[1,3-b]oxazine-1,5-dione 4a even using triethylamine in chloroform (Figure 2, entries 1–4), and the presence of a Lewis acid additive proved beneficial for the reaction outcome (entries 5–9).

With a catalytic amount (0.01 mol%) of iron(II) bromide as the most favorable additive, an increase in the reaction temperature (120 °C) led to the desired product with a good yield (79%, entry 10). We hypothesized that both the iron Lewis acid and higher temperature favored the key dehydration step. Attempts to decrease the amounts of both the catalyst and the additive (entries 11,12), and to improve the yield by adding a little excess of the alkynoic acid or changing the reaction concentration (entries 13–18) were made so that an excellent 93% yield was obtained by the optimized conditions of entry 17. Lower temperatures or shorter reaction times (entries 19,20) provided poorer results, and a series of blank experiments proved the need of all the ingredients, including Et3N as a base and FeBr2 as an additive, along with the palladium source (entries 21–23 vs. 17). In this regard, we were surprised to find that target 4a was isolated with a yield of 86% when complex 1 was replaced with Pd(OAc)2 (entry 28). Therefore, when the optimized conditions (Figure 2, entry 21) were applied to a number of commercially or readily available (Supplementary Material) alkynoic acids 2 and heterodinucleophiles 3, Pd(OAc)2 was also evaluated as a catalyst for the reaction.

| Entry | solv. (M) | [Pd] (mol%) | Base | Additive | T (°C) | t (h) | 4a (%) |
|-------|-----------|-------------|------|----------|--------|-------|--------|
| 1     | CHCl3 (0.1) | 1 (10-5) | EtN  | -        | 60     | 96    | 14     |
| 2     | CHCl3 (0.1) | Pd(OAc)2 (10-2) | EtN  | -        | 60     | 96    | -      |
| 3     | CHCl3 (0.1) | Pd(OAc)2 (10-2) | EtN  | -        | 120    | 96    | -      |
| 4     | CHCl3 (0.1) | PdCl2 (10-3) | EtN  | -        | 60     | 96    | -      |
| 5     | CHCl3 (0.1) | 1 (10-5) | EtN  | p-TsOH   | 60     | 96    | 15     |
| 6     | CHCl3 (0.1) | 1 (10-5) | EtN  | BF3O(C6H5)2 | 60     | 96    | 20     |
| 7     | CHCl3 (0.1) | 1 (10-5) | EtN  | AlCl3    | 60     | 96    | 27     |
| 8     | CHCl3 (0.1) | 1 (10-5) | EtN  | FeCl3    | 60     | 96    | 45     |
| 9     | CHCl3 (0.1) | 1 (10-5) | EtN  | FeBr2    | 60     | 96    | 48     |
| 10    | CHCl3 (0.1) | 1 (10-5) | EtN  | FeBr2    | 120    | 96    | 79     |
| 11    | CHCl3 (0.1) | 1 (10-4) | EtN  | FeBr2    | 120    | 96    | 39     |
| 12    | CHCl3 (0.1) | 1 (10-5) | EtN  | FeBr2    | 120    | 96    | 24     |
| 13    | CHCl3 (0.1) | 1 (10-5) | EtN  | FeBr2    | 120    | 96    | 69     |
| 14    | CHCl3 (0.1) | 1 (10-5) | EtN  | FeBr2    | 120    | 96    | 85     |
| 15    | CHCl3 (0.2) | 1 (10-5) | EtN  | FeBr2    | 120    | 96    | 85     |
| 16    | CHCl3 (0.02) | 1 (10-5) | EtN  | FeBr2    | 120    | 96    | <5     |
| 17    | CHCl3 (0.5) | 1 (10-5) | EtN  | FeBr2    | 120    | 96    | 93     |
| 18    | CHCl3 (1) | 1 (10-3) | EtN  | FeBr2    | 120    | 96    | 59     |
| 19    | CHCl3 (0.5) | 1 (10-5) | EtN  | FeBr2    | 120    | 72    | 71     |
| 20    | CHCl3 (0.5) | 1 (10-5) | EtN  | FeBr2    | 70     | 96    | 57     |
| 21    | CHCl3 (0.5) | 1 (10-5) | EtN  | FeBr2    | 120    | 96    | 13     |
| 22    | CHCl3 (0.5) | 1 (10-5) | EtN  | FeBr2    | 120    | 96    | <5     |
| 23    | CHCl3 (0.5) | -        | EtN  | FeBr2    | 120    | 96    | -      |
| 24    | CHCl3 (0.5) | Pd(OAc)2 (10-2) | EtN  | FeBr2    | 120    | 96    | 86     |
| 25    | CHCl3 (0.5) | Pd(OAc)2 (10-4) | EtN  | FeBr2    | 120    | 96    | <5     |
| 26    | CHCl3 (0.5) | Pd(OAc)2 (10-4) | EtN  | FeBr2    | 120    | 96    | -      |

* Reaction conditions: 2a (0.2 mmol), 3a (0.2 mmol), base (2 mol%), additive (10-3 mol%). * Isolated yields. * FeBr2 (10-4 mol%). * 2a (0.3 mmol), 3a (0.2 mmol). * 2a (0.2 mmol), 3a (0.3 mmol).

Figure 2. Palladium-catalyzed formation of benzo[d]pyrrolo[2,1-b]oxazine-1,5-dione 4a. Selected optimization experiments.*
Benzopyrrolo[1,3]oxazine-1,5-diones and benzopyrido[1,3]oxazine-1,6-diones 4a–e were prepared in good to excellent yields from anthranilic acid 3a and several terminal and internal alkynoic acids 2 (Figure 3). In addition to the easy formation of tetra-cyclic 4c from o-ethynylbenzoic acid and the high diastereoselectivity with which 2-hexylbenzo[d]pyrrolo[1,3]oxazine-1,5-dione 4b was obtained, the use of internal alkyne 5-phenylpent-4-ynoic acid to generate 3a-benzyl derivative 4e, and the preparation of pyrido[1,3]oxazine-1,6-dione 4d should be pointed out on account of the reduced reactivity of 5-hexynoic acid in comparison with pentynoic acids [28–30]. An even more interesting observation was that Pd(OAc)$_2$ failed to provide target products 4b–e in acceptable yields.

![Catalysts 2022, 12, x FOR PEER REVIEW](image)

Figure 3. Palladium-catalyzed cascade reaction between alkynoic acids and o-aminobenzoic acid or o-aminobenzenesulfonamide.

The same trend was observed for the formation of benzopyrrolo[1,2,4]thiadiazin-1-one and benzopyrido[1,2,4]thiadiazinone-5,5-dioxides 4f–h, prepared in good to excellent yields only when the system 1/FeBr$_2$/Et$_3$N was employed (Figure 3).

Much effort has been devoted to the synthesis of benzopyrrolo[1,2,4]thiadiazine-5,5-dioxides [31–35] due to their nootropic, neuroprotective and cognition-enhancing properties as positive allosteric modulators of the AMPA receptor [36,37]. With regard to 4g, it is the first benzopyrido[1,2,4]thiadiazinone-5,5-dioxide synthesized so far.

Structure analysis of monocrystals of 4a and 4e revealed that both have the same crystal system and space group (orthorhombic Pbcn). The presence of the C3a quaternary center (C-11) is responsible for the lack of coplanarity of oxazine and pyrrole rings, as shown by the C1-O1-C11-N1 and C7-N1-C11-C10 torsion angle values of $-$53.4–39.6$^\circ$ and 165.1–164.4$^\circ$, respectively. Only the R enantiomer of sultam 4g crystallized in the monoclinic system (Cc) leaving the other C-5 isomer in an amorphous state (Figure 4).
Figure 4. Molecular structure of benzopyrrolo[1,3]oxazine-1,5-diones 4a and 4e and benzopyrido[1,2,4]thiazinone-5,5-dioxide 4g with the atomic numbering scheme. Thermal ellipsoids are given at the 50% probability level.

Several diamines 5 were also reacted with alkynoic acids 2. Palladacycle 1 catalyzed cascade process on a general basis, whereas Pd(OAc)$_2$ did not provide most of the target tri- and tetracycles 6. In fact, only quinazolinones 6a and 6c were obtained when using the latter commercially available palladium source, although with much inferior yields (Figure 5).

Figure 5. Palladium-catalyzed cascade reaction between alkynoic acids and diamines.

As in the case of derivatives 4, the reason probably lies in the inability of palladium(II) acetate to catalyze the initial cycloisomerization step at such low catalyst levels. By using remarkably active palladacycle 1, pyrrolo-, isoindolo- and pyrido[2,1-b]quinazolinones 6a–d were regio-selectively prepared from o-aminobenzylamine 5a. As in the case of anthranilic acid 3a or 2-aminobenzenesulfonamide 3b, the use of internal alkynes did not hinder the reaction, and 3a-benzyl derivative 6d was obtained in good yield. Besides,

\[ R^1 COOH \quad R \quad CH_2 COOH \]

\[ \text{Y} = \text{CH, N} \]

\[ n = 0, 1 \]

\[ 1 \text{ (0.01 mol\%), FeBr}_2 \text{ (0.01 mol\%), } \]

\[ \text{Et}_2\text{N} \text{ (2 mol\%), CHCl}_3 \text{ (0.5 M)} \]

\[ \text{1 (0.01 mol\%) FeBr}_2 \text{ (0.01 mol\%), Et}_2\text{N} \text{ (2 mol\%), CHCl}_3 \text{ (0.5 M)} \]

\[ 6 \text{ (57\%) \text{ a} 22\% \text{ b} } \]

\[ 6a \text{ (65\%) \text{ a} 61\% \text{ b} } \]

\[ 6b \text{ (82\%) \text{ a} 61\% \text{ b} } \]

\[ \text{6c (57\%) a 22% b} \]

\[ 6d \text{ (81\%) a 66\% b} \]

\[ 6e \text{ (74\%) a 66\% b} \]

\[ 6f \text{ (75\%) a 66\% b} \]

\[ 6g \text{ (90\%) a 66\% b} \]

\[ ^a \text{Isolated yield. Reaction conditions: 2 (0.2 mmol), 3 (1.5 equiv.), 1 (10^{-2} \text{ mol\%)}, FeBr}_2 \text{ (10^{-2} \text{ mol\%)}, } \]

\[ \text{Et}_2\text{N} \text{ (2 mol\%), CHCl}_3 \text{ (0.4 mL per mmol of 2), 120 } ^\circ\text{C, 96 h.} \]

\[ ^b \text{Isolated yield. Reaction conditions: 3 (0.2 mmol), 2 (1.5 equiv.), Pd(OAc)$_2$ (10^{-2} \text{ mol\%)}, FeBr}_2 \text{ (10^{-2} \text{ mol\%)}, Et}_2\text{N} \text{ (2 mol\%), CHCl}_3 \text{ (0.4 mL per mmol of 2), 120 } ^\circ\text{C, 96 h.} \]
reaction of 5a with 5-hexynoic acid provided pyrido[2,1-b]quinazolin-9-one 6c. So far, this compound had been prepared in reasonable yield only from 5-oxohexanoic acid by a Meyers' lactamization [38].

Benzo[d]pyrrolo[1,2-a]imidazol-1-one 6a and benzo[4,5]imidazo[2,1-a]isoindol-11-one 6f (akin to AKR1C3 inhibitor in Figure 1) were prepared by reaction with o-phenylene diamine 5b. Interestingly, a higher yield was obtained for new pyrroloimidazo[4,5-b]pyridin-6-one 6g from 2,3-diaminopyridine 5c. A significantly greater anticonvulsant effect than currently marketed valproate has been described for several structurally related pyrroloimidazopyridine derivatives prepared by condensation between 2,3-diaminopyridine and 3-acylpropionic acids [39–41]. Considering the latter result from 5c, a comparison of the reaction yields from dinucleophiles 3a, b and 5a–c with 4-pentyenoic acid 2a led to the conclusion that the reaction is favored by the use of non-symmetric dinucleophiles.

Several experiments were then carried out in order to shed light on the role of complex 1 in the reaction mechanism. Taking the reaction leading to the formation of benzopyrrolo[1,3]oxazine-1,5-dione 4a as a model example, a plot of the conversion of anthranilic acid 3a vs. time showed neither sigmoidal shape nor induction time (Figure 6).

In addition, the latter reaction was also conducted in the presence of substoichiometric and overstoichiometric amounts of a number of known poisoning agents for palladium nanoparticles and other palladium(0) heterogeneous catalysts, including the mercury drop test (Table 1). Not the slightest inhibition or poisoning effect was observed in our case, as expected for a fully homogeneous catalyst system [42–47].

Table 1. Summary of poisoning experiments a.

| Entry | Poisoning Additive | 4a (%) b |
|-------|--------------------|----------|
| 1     | Hg (one drop)      | 99       |
| 2     | CS2 (0.5 equiv. per metal atom) | 99 |
| 3     | CS2 (2.0 equiv. per metal atom) | 98 |
| 4     | PPh3 (0.03 equiv. per metal atom) | 99 |
| 5     | PPh3 (0.3 equiv. per metal atom) | 99 |
| 6     | PPh3 (4.0 equiv. per metal atom) | 99 |
| 7     | Py (150 equiv. per metal atom) c | 98 |
| 8     | PVPy (300 equiv. per metal atom) d | 99 |

a Reaction conditions: 3a (0.2 mmol), 2a (1.5 equiv.), 1 (10−2 mol%), FeBr2 (10−2 mol%), Et3N (2 mol%), CHCl3 (0.4 mL per mmol of 2), 120 °C, 96 h. b NMR yields determined using 3,4,5-trichloropyridine as an internal standard. c Py: Pyridine. d PVPy: Polyvinylpyridine.

Moreover, transmission electron microscopy (TEM) analysis of the reaction mixture from 3a + 2a -> 4a, combined with energy dispersive X-ray microanalysis revealed the presence of some scattered iron nanoparticles (average size 8 nm) but no trace of palladium nanoparticles (Figure 7).
Table 1. Summary of poisoning experiments

| Entry | Poisoning agent | Yield (%) | Carbon | Nitrogen |
|-------|-----------------|-----------|--------|----------|
| a     | Cu              | 90        | 0.5    | 0.3      |
| b     | Fe              | 95        | 0.5    | 0.2      |
| c     | Hg              | 98        | 0.5    | 0.4      |

UPLC-ESI analysis of a sample taken from the reaction mixture (2a + 3a -> 4a) after 12 h of reaction not only provided evidence of the presence of several transient intermediates related to the ones postulated in Scheme 1, but also of the participation of a number of palladium and iron species displayed in Scheme 2 (see Supplementary Material for further details), thus supporting our hypothesis on the crucial role of such ingredients in the cascade reaction. On the basis of the detection of the above intermediates, a revised catalytic cycle was tentatively proposed (Scheme 2). Interaction of alkynoic acid 2a with cationic 1′ to form complex A activates the alkyne for the triethylamine-promoted cycloisomerization process that generates intermediate B, which upon protonation and interaction with Lewis’s acids 1′ and FeBr₂ produces transient species C. Ring-opening amidation with α-amino derivative 3a leads to activated ketoamides D, which upon cyclization form hydroxypyrrrolidinones E. After dehydration, the resulting N-acyliminium intermediates F undergo a final lactamization step to provide oxazinanone derivative 4a. According to the transient species detected by ESI-mass spectrometry (Supplementary Material), it seems that although the palladium catalyst is essential to initiate the cycloisomerization step and thus to promote the reaction, the iron additive facilitates several nucleophilic addition and dehydration steps via Lewis acid activation.

Finally, methylidene lactone 7 was prepared using catalyst 1, and then reacted with anthranilic acid 3a in the presence and absence of the optimized catalyst and additives. Target benzopyrrolo[1,3]oxazine-1,5-dione 4a was obtained in good yield (90%, Scheme 3) only when both complex 1 and FeBr₂ were employed, whereas reactions lacking any of these ingredients led to negligible results (yield of 4a < 15%) (see Supplementary Material for further details), thus offering further support for the proposed reaction pathway.
Scheme 2. Revised catalytic cycle for the cascade reaction catalyzed by the \( \text{I}/\text{FeBr}_3/\text{Et}_3\text{N} \) system.

Scheme 3. Reaction of methylene lactone 7 with anthranilic acid 3a under optimized conditions.

3. Materials and Methods

3.1. General Information

Commercially available reagents were used throughout without purification unless otherwise stated. \(^1\)H and \(^{13}\)C NMR spectra were recorded on a Bruker AC-300 instrument (300 MHz for \(^1\)H and 75.4 MHz for \(^{13}\)C) at 20 °C. Chemical shifts (d) are given in ppm downfield from Me\(_4\)Si and are referenced as internal standard to the residual solvent (unless indicated) CDCl\(_3\) (d = 7.26 for \(^1\)H and d = 77.00 for \(^{13}\)C). Coupling constants, J, are reported in hertz (Hz). Melting points were determined in a capillary tube and are uncorrected. TLC was carried out on SiO\(_2\) (silica gel 60 F254, Merck), and the spots were located with UV light. Flash chromatography was carried out on SiO\(_2\) (silica gel 60, Merck, 230–400 mesh ASTM).

Drying of organic extracts during work-up of reactions was performed over anhydrous Na\(_2\)SO\(_4\). Evaporation of solvents was accomplished with a Büchi rotatory evaporator. MS spectra were recorded on an Agilent 5975 mass spectrometer under electronic impact (EI) conditions or on an Acquity UPLC-Spectrometer of Mass QTOF from Waters under electrospray ionization (ESI). HRMS were recorded using a Micromass GCT spectrometer by electronic impact (EI) or electrospray ionization (ESI). Single crystal X-ray intensity data were collected on an Agilent Technologies Super-Nova diffractometer, which was equipped with monochromated Cu \(\lambda\) radiation (\(\lambda = 1.54184\) Å) and Atlas CCD detector. A measurement was carried out at 100(2) K with the help of an Oxford Cryostream 700 PLUS temperature device. Data frames were processed (united cell determination, analytical absorption correction with face indexing, intensity data integration and correction for Lorentz and polarization effects) using the Crystals software package [48]. The structure was solved using Olex2 [49] and refined by full-matrix least-squares with SHELXL-97 [50].
3.2. General Procedure for Complex 1-Catalyzed Cascade Reaction between Alkynoic Acids and Heterodinucleophiles

Alkynoic acid 2 (0.2 mmol) and heterodinucleophile 3 or 5 (0.3 mmol) were charged in a heavy-wall pressure tube at room temperature with a magnetic stir bar under argon. Then, triethylamine (0.56 mL, 4.0 × 10^{-3} mmol), a solution of FeBr₃ (30 µL of a 0.67 M solution in CHCl₃, 2 × 10^{-5} mmol), a solution of NNC pincer 1 (30 µL of a 0.67 M solution in CHCl₃, 2 × 10^{-5} mmol) and CHCl₃ (0.34 mL) were added, the tube closed, and the mixture was heated in an oil bath at 120 °C for 96 h. After cooling, the mixture was concentrated in vacuo and purified by flash column chromatography using hexane/ethyl acetate as eluent to provide polycyclic compounds 4/6.

3a-Methyl-3a-dihydro-5H-benzo[d]pyrrolo[2,1-b][1,3]oxazine-1,5(2H)-dione (4a). The general procedure was followed, and compound 4a was obtained as colorless prisms (40.4 mg, 93%). m.p. 143–147 °C (CHCl₃)(Lit. [10] 165–167 °C); Its NMR spectra were consistent with published data [10]. ¹H NMR (CDCl₃) δ 8.12–8.05 (m, 2H, H_arom), 7.71–7.65 (m, 1H, H_arom), 7.34 (t, J = 7.7 Hz, 1H, H_arom), 3.84–3.37 (m, 4H, CH₂), 1.70 (s, 3H, CH₃). ¹³C NMR (CDCl₃) δ 171.6 (NCO), 161.6 (COO), 136.2 (qC)

Heterodinucleophile

4b

The general procedure was followed, and compound 4b was obtained as a yellow powder (46.1 mg, 61%). m.p. 138–142 °C (CHCl₃)(Lit. [54] 145–148 °C (PrOH)); Its NMR spectra were consistent with published data [15]. ¹H NMR (CDCl₃) δ 8.16 (d, J = 7.9, 1.3 Hz, 1H, H_arom), 7.96 (d, J = 7.5 Hz, 1H, H_arom), 7.81–7.71 (m, 3H, H_arom), 7.68–7.61 (m, 1H, H_arom), 7.40–7.35 (m, 1H, H_arom), 1.95 (s, 3H, CH₃). ¹³C NMR (CDCl₃) δ 164.7 (NCO), 162.0 (COO), 144.20, 136.2 (qC_arom), 135.8, 133.9, 130.9, 130.6 (C_arom), 130.0 (qC_arom), 125.5, 124.7, 122.5 (C_arom), 117.7 (qC_arom), 94.6 (qC), 40.6 (CH₂), 38.2 (CH), 31.9 (CH₂), 31.6 (CH₂), 28.9 (CH₂), 27.1 (CH₂), 26.2 (CH₂), 22.5 (CH₃), 14.0 (CH₃).

6a-Methyl-5H-benzo[4,5][1,3]oxazino[2,3-a]isoindole-5,11(6aH)-dione (4c). The general procedure was followed, and compound 4c was obtained as a yellow powder (46.1 mg, 87%); m.p. 138–142 °C (CHCl₃)(Lit. [54] 145–148 °C (PrOH)); Its NMR spectra were consistent with published data [15]. ¹H NMR (CDCl₃) δ 8.16 (d, J = 7.9, 1.3 Hz, 1H, H_arom), 8.12 (d, J = 8.2 Hz, 1H, H_arom), 7.96 (d, J = 7.5 Hz, 1H, H_arom), 7.81–7.71 (m, 3H, H_arom), 7.68–7.61 (m, 1H, H_arom), 7.40–7.35 (m, 1H, H_arom), 1.95 (s, 3H, CH₃). ¹³C NMR (CDCl₃) δ 164.7 (NCO), 162.0 (COO), 144.20, 136.2 (qC_arom), 135.8, 133.9, 130.9, 130.6 (C_arom), 130.0 (qC_arom), 125.5, 124.7, 122.5 (C_arom), 117.7 (qC_arom), 94.6 (qC), 40.6 (CH₂), 38.2 (CH), 31.9 (CH₂), 31.6 (CH₂), 28.9 (CH₂), 27.1 (CH₂), 26.2 (CH₂), 22.5 (CH₃), 14.0 (CH₃).

4a-Methyl-2,3,4a-tetrahydro-1H,6H-benzo[d]pyrido[2,1-b][1,3]oxazine-1,6-dione (4d). The general procedure was followed, and compound 4d was obtained as a white powder (28.8 mg, 61%); m.p. 70–72 °C (CHCl₃)(Lit. [10] 66–68 °C); Its NMR spectra were consistent with published data [10]. ¹H NMR (CDCl₃) δ 8.06 (dd, J = 7.8, 1.5 Hz, 1H, H_arom), 7.78 (dd, J = 8.0, 0.9 Hz, 1H, H_arom), 7.64 (td, J = 7.8, 1.5 Hz, 1H, H_arom), 7.35 (td, J = 8.0, 0.9 Hz, 1H, H_arom), 2.72–2.53 (m, 2H, CH₂), 2.49–2.35 (m, 1H, CH₂), 2.21–2.01 (m, 2H, CH₂), 1.96–1.79 (m, 1H, CH₂), 1.62 (s, 3H, CH₃). ¹³C NMR (CDCl₃) δ 169.2 (NCO), 162.5 (COO), 138.6
3a-Benzyl-3,3a-dihydro-5H-benzo[d]pyrrolo[2,1-b][1,3]oxazine-1,5(2H)-dione (4e). The general procedure was followed, and compound 4e was obtained as colorless prisms (43.9 mg, 75%); m.p. 142–146 °C (CHCl₃); ¹H NMR (CDCl₃) δ 8.21 (d, J = 8.0 Hz, 1H, Hₐrom); 8.14 (dd, J = 7.8, 1.4 Hz, 1H, Hₐrom), 7.77 (td, J = 8.2, 1.5 Hz, 1H, Hₐrom), 7.37 (td, J = 7.8, 0.9 Hz, 1H, Hₐrom), 7.28 (dd, J = 6.6, 3.9 Hz, 3H, H₂ₐrom), 7.04 (dd, J = 6.5, 2.9 Hz, 2H, H₂ₐrom), 3.36 (d, J = 13.8 Hz, 1H, CH₂), 3.11 (d, J = 13.7 Hz, 1H, CH₂), 2.65–2.29 (m, 3H, CH₂), 1.73–1.50 (m, 1H, CH₂); ¹³C NMR (CDCl₃) δ 172.0 (NCO), 161.4 (COO), 136.3 (qCₐrom), 135.9 (Cₐrom), 133.0 (qCₐrom), 130.6, 129.9, 128.9, 127.9, 125.8, 120.7 (Cₐrom), 116.3 (qCₐrom), 96.8 (qC), 42.6 (CH₂), 30.2 (CH₂), 29.5 (CH₂); HRMS (m/z): [M + H]⁺ calc. for C₁₈H₁₆N₂O₃: 294.1130; found: 294.1129.

3a-Methyl-2,3,3a,4-tetrahydro-1H-benzo[e]pyrrolo[2,1-c][1,2,4]thiadiazin-1-one 5,5-dioxide (4f). The general procedure was followed, and compound 4f was obtained as colorless prisms (47.4 mg, 94%); m.p. 189–192 °C (CHCl₃); ¹H NMR (DMSO-d₆) δ 8.55 (s, 1H, NH), 8.28 (dd, J = 8.4, 0.8 Hz, 1H, Hₐrom), 7.81 (dd, J = 7.9, 1.4 Hz, 1H, Hₐrom), 7.73–7.55 (m, 1H, Hₐrom), 7.38 (td, J = 7.8, 1.0 Hz, 1H, Hₐrom), 2.77 (dt, J = 17.2, 10.0 Hz, 1H, CH₂), 2.31–2.18 (m, 3H, CH₂), 1.58 (s, 3H, CH₃); ¹³C NMR (DMSO-d₆) δ 172.3 (NCO), 133.6 (Cₐrom), 132.9, 127.9 (qCₐrom), 125.6, 124.7, 122.2 (Cₐrom), 78.1 (qC), 33.2 (CH₂), 29.6 (CH₂), 24.5 (CH₃); HRMS (m/z): [M + H]⁺ calc. for C₁₁H₁₃N₂O₂S: 253.0647; found: 253.0640.

6a-Methyl-6a,7,8,9-tetrahydrobenzo[e]pyrido[2,1-c][1,2,4]thiadiazin-10(6H)-one 5,5-dioxide (4g). The general procedure was followed, and compound 4g was obtained as yellow prisms (33.5 mg, 63%); m.p. 196–199 °C (CHCl₃); ¹H NMR (CDCl₃) δ 7.81 (d, J = 7.7 Hz, 1H, Hₐrom), 7.58 (d, J = 3.7 Hz, 2H, H₂ₐrom), 7.44–7.36 (m, 1H, Hₐrom), 5.17 (bs, 1H, NH), 2.62 (t, J = 6.3 Hz, 2H, CH₂), 2.23–2.06 (m, 3H, CH₂), 1.95–1.80 (m, 1H, CH₂), 1.52 (s, 3H, CH₃); ¹³C NMR (CDCl₃) δ 170.0 (NCO), 135.4 (qCₐrom), 134.5 (qCₐrom), 132.4, 129.3, 127.0, 123.4 (Cₐrom), 76.1 (qC), 38.1, 33.3 (CH₂), 27.6 (CH₃), 16.2 (CH₂); HRMS (m/z): [M + H]⁺ calc. for C₁₂H₁₅N₂O₂S: 267.0803; found: 267.0802.

3a-Benzyl-2,3,3a,4-tetrahydro-1H-benzo[e]pyrrolo[2,1-c][1,2,4]thiadiazin-1-one 5,5-dioxide (4h). The general procedure was followed, and compound 4h was obtained as a white powder (47.9 mg, 73%); m.p. 194–196 °C (CHCl₃); ¹H NMR (CDCl₃) δ 8.32 (d, J = 8.4 Hz, 1H, Hₐrom), 7.80 (d, J = 7.9 Hz, 1H, Hₐrom), 7.61 (t, J = 7.4 Hz, 1H, Hₐrom), 7.26–7.30 (m, 4H, Hₐrom), 7.04–7.07 (m, 2H, H₂ₐrom), 5.77 (bs, 1H, NH), 3.54 (d, J = 14.1 Hz, 1H, CH₂), 3.06 (d, J = 14.1 Hz, 1H, CH₂), 2.55–2.46 (m, 1H, CH₂), 2.24–1.99 (m, 2H, CH₂), 1.46–1.31 (m, 1H, CH₂); ¹³C NMR (CDCl₃) δ 174.2 (NCO), 133.7 (Cₐrom), 132.5 (qCₐrom), 130.1, 128.9 (Cₐrom), 127.9 (qCₐrom), 127.8, 125.8, 124.7, 122.8 (Cₐrom), 80.3 (qC), 42.1 (CH₂), 31.3 (CH₂), 29.6 (CH₂); HRMS (m/z): [M + H]⁺ calc. for C₁₇H₁₇N₂O₂S: 329.0960; found: 329.0957.

3a-Methyl-3,3a,4,9-tetrahydropyrrolo[2,1-b]quinazolin-1(2H)-one (6a). The general procedure was followed, and compound 6a was obtained as yellow prisms (38.4 mg, 95%); m.p. 131–134 °C (CHCl₃)[Lit. 8] 138–140 °C); Its NMR spectra were consistent with published data [8]. ¹H NMR (CDCl₃) δ 7.10–6.96 (m, 1H, Hₐrom), 6.78 (t, J = 7.4 Hz, 1H, Hₐrom), 6.56 (d, J = 8.0 Hz, 1H, Hₐrom), 5.02 (d, J = 16.9 Hz, 1H, CH₂), 4.17 (d, J = 16.8 Hz, 1H, CH₂), 3.83 (bs, 1H, NH), 2.59–2.48 (m, 2H, CH₂), 2.25–1.97 (m, 2H, CH₂), 1.54 (s, 3H, CH₃); ¹³C NMR (CDCl₃) δ 174.2 (NCO), 141.8 (qCₐrom), 127.6, 126.9, 119.3 (Cₐrom), 117.4 (qCₐrom), 116.4 (Cₐrom), 71.9 (qC), 38.6 (CH₂), 32.9 (CH₂), 29.5 (CH₂), 25.6 (CH₃).

4b-Methyl-5,10-dihydroisindolo[1,2-b]quinazolin-12(4H)-one (6b). The general procedure was followed, and compound 6b was obtained as a brown powder (41.0 mg, 82%); m.p. 190–194 °C (CHCl₃)[Lit. 8] 222–224 °C); Its NMR spectra were consistent with published data [8]. ¹H NMR (CDCl₃) δ 7.88 (d, J = 7.4 Hz, 2H, Hₐrom), 7.63 (d, J = 4.0 Hz, 2H, Hₐrom), 7.58–7.48 (m, 1H, Hₐrom), 7.15–7.09 (m, 2H, Hₐrom), 6.88 (t, J = 7.4 Hz, 1H, Hₐrom), 6.69 (d, J = 8.0 Hz, 1H, Hₐrom), 5.32 (d, J = 16.8 Hz, 1H, CH₂), 4.45 (d, J = 17.1 Hz, 1H, CH₂), 3.02 (s, 3H, CH₃).
114.5 (C\textsubscript{1}H, H\textsubscript{1}H, H\textsubscript{1}H, 142.7, 128.6 (qC\textsubscript{1}H, CH\textsubscript{1}H, CH\textsubscript{1}H, 131.3 (qC\textsubscript{1}H, CH\textsubscript{1}H, CH\textsubscript{1}H, 125.2 (CH\textsubscript{1}H, 2.45–2.36 (m, 2H, CH\textsubscript{2}H)), 132.1, 130.7 (qC\textsubscript{1}H, 125.2, 120.1, 115.4, 110.6 (C\textsubscript{arom}), 85.6 (qC), 37.7 (CH\textsubscript{2}H), 33.6 (CH\textsubscript{2}H), 26.2 (CH\textsubscript{3}H)).

8a-Methyl-7,8,8a,9-tetrahydro-6H-pyrrolo[1′:2′:1,2]imidazo[4,5-b]pyridin-6-one (6g). The general procedure was followed, and compound 6g was obtained as a brown oil (34.0 mg, 90%); Its NMR spectra were consistent with published data [40]. 1H NMR (CDCl\textsubscript{3}) δ 7.75 (dd, J = 5.4, 1.2 Hz, 1H, H\textsubscript{arom}), 7.52 (dd, J = 7.4, 1.4 Hz, 1H, H\textsubscript{arom}), 6.66 (dd, J = 7.4, 5.5 Hz, 1H, H\textsubscript{arom}), 5.84 (bs, 1H, NH), 2.87–2.65 (m, 1H, CH\textsubscript{2}H), 2.60–2.38 (m, 3H, CH\textsubscript{2}H), 1.58 (s, 3H, CH\textsubscript{3}H); 13C NMR (CDCl\textsubscript{3}) δ 174.9 (NCO), 156.6 (qC\textsubscript{arom}), 142.8 (C\textsubscript{arom}), 122.5 (qC\textsubscript{arom}), 120.6, 114.5 (C\textsubscript{arom}), 83.3 (qC), 38.2 (CH\textsubscript{2}H), 32.5 (CH\textsubscript{2}H), 26.7 (CH\textsubscript{3}H).

4. Conclusions

To sum up, an alternative catalyst system for the cascade reaction between alkynoic acids and heterodinucleophiles is presented. This palladium-based system is based on the use of very small amounts of a NNC pincer complex, thus providing a more efficient approach to polycyclic structures of interest. Good to excellent yields are obtained in all cases by this particularly active system, which according to a number of mechanistic studies
participates as a fully homogenous catalyst. A more nuanced mechanism describing the role of the metal species and transient intermediates detected by UPLC-ESI is also proposed.

**Supplementary Materials:** The following are available online at https://www.mdpi.com/article/10.3390/catal12020127/s1, synthesis of 5-phenylpent-4-ynoic acid, structure factor tables, additional experiments, ESI-MS results and scans of NMR spectra (PDF).

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**References**

1. Gopalaiah, K.; Choudhary, R. Synthesis of Kröhnke pyridines through iron-catalyzed oxidative condensation/double alkynylation/amination cascade strategy. *Tetrahedron* 2021, 98, 132429. [CrossRef]

2. Liao, X.R.; Zhou, F.L.; Bin, Z.Y.; Yang, Y.D.; You, J.S. Palladium-Catalyzed Cascade Dearomatic Spirocyclization and C-H Annulation of Aromatic Halides with Alkynes. *Org. Lett.* 2021, 23, 5203–5207. [CrossRef]

3. Yang, X.H.; Huang, J.; Wang, F.; Liu, Z.L.; Li, Y.J.; Tao, C.A.; Wang, J.P. Copper-catalyzed alkynylation/annulation cascades of N-alllyl ynamides: Regioselective access to medium-sized N-heterocycles. *Org. Chem. Front.* 2021, 8, 18–24. [CrossRef]

4. Yang, Y.Z.; He, D.L.; Li, J.H. Rhodium-Catalyzed Reductive trans-Alkylation of Internal Alkynes via a Formal Carborhodation/C-H Carbonylation Cascade. *Org. Lett.* 2021, 23, 5039–5043. [CrossRef] [PubMed]

5. Yang, T.; Campbell, L.; Dixon, D.J. A Au(I)-Catalyzed N-Acyliminium Cyclization Cascade. *J. Am. Chem. Soc.* 2007, 129, 12070–12071. [CrossRef]

6. Muratore, M.E.; Holloway, C.A.; Pilling, A.W.; Storer, R.I.; Trevitt, G.; Dixon, D.J. Enantioselective Brønsted Acid-Catalyzed N-Acyliminium Cyclization Cascades. *J. Am. Chem. Soc.* 2009, 131, 10796–10797. [CrossRef]

7. Yang, T.; Ferrali, A.; Campbell, L.; Dixon, D.J. Combination iminium, enamine and copper(I) cascade catalysis: A carbnoannulation for the synthesis of cyclopentenes. *Chem. Commun.* 2008, 25, 2923–2925. [CrossRef] [PubMed]

8. Patil, N.T.; Mutyala, A.K.; Lakshmi, P.G.V.; Gajula, B.; Sridhar, B.; Pottireddygari, G.R.; Rao, T.P. Au(I)-Catalyzed Cascade Reaction Involving Formal Double Hydroamination of Alkynes Bearing Tethered Carboxylic Groups: An Easy Access to Fused Dihydrobenzimidazoles and Tetrahydroquinazolines. *J. Org. Chem.* 2010, 75, 5963–5975. [CrossRef]

9. Patil, N.T.; Shinde, V.S.; Sridhar, B. Relay Catalytic Branching Cascade: A Technique to Access Diverse Molecular Scaffolds. *Angew. Chem. Int. Ed.* 2013, 52, 2251–2255. [CrossRef]

10. Feng, E.; Zhou, Y.; Zhang, D.; Zhang, L.; Sun, H.; Jiang, H.; Liu, H. Gold(I)-Catalyzed Tandem Transformation: A Simple Approach for the Synthesis of Pyrrolo/Pyrido[2,1-a][1,3]benzoxazines and Pyrrolo/Pyrido[2,1-a]quinazolinones. *J. Org. Chem.* 2010, 75, 3274–3282. [CrossRef]

11. Zhou, Y.; Zhai, Y.; Ji, X.; Liu, G.; Feng, E.; Ye, D.; Zhao, L.; Jiang, H.; Liu, H. Gold(I)-Catalyzed One-Pot Tandem Coupling/Cyclization: An Efficient Synthesis of Pyrrolo-/Pyrido[2,1-b][1,3]oxazin-1-ones. *Adv. Synth. Catal.* 2010, 352, 373–378. [CrossRef]

12. Zhou, Y.; Li, J.; Ji, X.; Zhou, W.; Zhang, X.; Qian, W.; Jiang, H.; Liu, H. Silver- and Gold-Mediated Domino Transformation: A Strategy for Synthesizing Benzo[e]indolo[1,2-a]pyrrolo/pyrido[2,1-c][1,4]diazepine-3,9-diones. *J. Org. Chem.* 2011, 76, 1239–1249. [CrossRef]

13. Feng, E.; Zhou, Y.; Zhao, F.; Chen, X.; Zhang, L.; Jiang, H.; Liu, H. Gold-catalyzed tandem reaction in water: An efficient and convenient syn-thesis of fused polycyclic indoles. *Green Chem.* 2012, 14, 1888–1895. [CrossRef]

14. Ji, X.; Zhou, Y.; Wang, L.; Zhao, L.; Jiang, H.; Liu, H. Au(I)/Ag(I)-catalyzed cascade approach for the synthesis of benzo[4,5]imidazo[1,2-c]pyrrolo[1,2-a]quinazolinones. *J. Org. Chem.* 2013, 78, 4312–4318. [CrossRef] [PubMed]

15. Qiao, J.; Jia, X.; Li, P.; Liu, X.; Zhao, J.; Zhou, Y.; Wang, J.; Liu, H.; Zhao, F. Gold-catalyzed Rapid Construction of Nitrogen-containing Heterocyclic Compound Library with Scaffold Diversity and Molecular Complexity. *Adv. Synth. Catal.* 2019, 361, 1419–1440. [CrossRef]

16. Jia, X.; Li, P.; Liu, X.; Lin, J.; Chu, Y.; Yu, J.; Wang, J.; Liu, H.; Zhao, F. Green and Facile Assembly of Diverse Fused N-Heterocycles Using Gold-Catalyzed Cascade Reactions in Water. *Molecules* 2019, 24, 988. [CrossRef]
17. Zhou, Y.; Zhai, Y.; Ji, X.; Liu, G.; Feng, E.; Ye, D.; Zhao, L.; Jiang, H.; Liu, H. Gold-Catalyzed One-Pot Cascade Construction of Highly Functionalized Pyrrole[1,2-e]quinolin-1(2H)-ones. *J. Org. Chem.* 2009, 74, 7344–7348. [CrossRef]

18. Naidu, S.; Reddy, S.R. Copper-catalyzed tandem reaction in ionic liquid: An efficient reusable catalyst and solvent media for the synthesis of fused poly heterocyclic compounds. *RSC Adv.* 2016, 6, 62742–62746. [CrossRef]

19. Naidu, S.; Reddy, S.R. A Green and Recyclable Copper and Ionic Liquid Catalytic System for the Construction of Polyheterocyclic Compounds via One-pot Tandem Coupling Reaction. *ChemistrySelect* 2017, 2, 1196–1201. [CrossRef]

20. Zheng, Y.; Liu, J.; Lei, X. Ru-Catalyzed cascade reaction of α,ω-alkynoic acids and arylethylamines towards the synthesis of aryl-fused hetero-cycles. *Org. Chem. Front.* 2020, 7, 660–665. [CrossRef]

21. Kshirsagar, U.A. Recent developments in the chemistry of quinazolinone alkaloids. *Org. Biomol. Chem.* 2015, 13, 9336–9352. [CrossRef] [PubMed]

22. Brožić, P.; Turk, S.; Adeniji, A.O.; Konc, J.; Janežič, D.; Penning, T.M.; Rižner, T.L.; Gobec, S. Selective Inhibitors of Aldo-Keto Reductases AKR1C1 and AKR1C3 Discovered by Virtual Screening of a Fragment Library. *J. Med. Chem.* 2012, 55, 7417–7424. [CrossRef]

23. Herrero, M.T.; Díaz de Sarralde, J.; SanMartin, R.; Bravo, L.; Dominguez, E. Cesium Carbonate-Promoted Hydroamination of Alkynes: En-amides, Indoles and the Effect of Iron(III) Chloride. *Adv. Synth. Catal.* 2012, 354, 3054–3064. [CrossRef]

24. Conde, N.; SanMartin, R.; Herrero, M.T.; Dominguez, E. Palladium NNC Pincer Complex as an Efficient Catalyst for the Cycloisomerization of Alkynes. *Adv. Synth. Catal.* 2016, 358, 3283–3292. [CrossRef]

25. Sheldon, R.A. Fundamentals of green chemistry: Efficiency in reaction design. *Chem. Soc. Rev.* 2012, 41, 1437–1451. [CrossRef]

26. Jeon, S.; Li, H.; Walsh, P.J. A Green Chemistry Approach to a More Asymmetric Catalytic System: Solvent-Free and Highly Concentrated Alkyl Additions to Ketones. *J. Am. Chem. Soc.* 2005, 127, 16416–16425. [CrossRef]

27. Mahmoud, M.A.; El-Sayed, M.A. Enhancing Catalytic Efficiency of Hollow Palladium Nanoparticles by Photothermal Heating of Gold Nano-particles Added to the Cavity: Palladium–Gold Nanorattles. *ChemCatChem* 2014, 6, 3540–3546. [CrossRef]

28. Nebra, N.; Monot, J.; Shaw, R.; Martin-Vaca, B.; Bourissou, D. 1,3-Bis(thiophosphinoyl)indene: A Unique and Versatile Scaffold for Original Polymeric Complexes. *ACS Catal.* 2013, 3, 2930–2934. [CrossRef]

29. Lambert, C.; Utimoto, K.; Nozaki, H. Palladium(II) catalyzed cyclization of alkynoic acids. *Tetrahedron Lett.* 1984, 25, 5323–5326. [CrossRef]

30. Watanabe, T.; Ishii, Y.; Ishikawa, K.; Hidai, M. A Novel Catalyst with a Cuboidal PdMo3S4 Core for the Cyclization of Alkynoic Acids to Enol Lactones. *Angew. Chem. Int. Ed.* 1996, 35, 2123–2124. [CrossRef]

31. Cordi, A.; Spedding, M.; Serkiz, B.; Lepagnol, J.; Desos, P.; Morain, P. Preparation of (3αS)-5,5-Dioxo-2,3,3a,4-tetrahydro-1H-pyrrolo[2,1-c][1,2,4]benzothiadiazine AMPA Receptor Agonist. European Patent EP692484, 17 January 1996.

32. Cordi, A.; Spedding, M.; Serkiz, B.; Lepagnol, J.; Desos, P.; Morain, P. Preparation of (3αS)-5,5-Dioxo-2,3,3a,4-tetrahydro-1H-pyrrolo[2,1-c][1,2,4]benzothiadiazine AMPA Receptor Agonist. *J. Med. Chem.* 2008, 51, 4994–4996. [CrossRef]

33. Carrozzi, M.M.; Battisti, U.M.; Canevascini, G.; Puia, G.; Ravazzini, F.; Falchichio, A.; Perrone, S.; Citti, C.; Jozwiak, K.; Braghiroli, D.; et al. Design, stereoselective synthesis, configurational stability and biological activity of 7-chloro-9-(furan-3-yl)-2,3,3a,4-tetrahydro-1H-pyrrolo[2,1-c][1,2,4]benzothiadiazine 5,5-dioxide. *Org. Biomol. Chem.* 2017, 15, 3283–3292. [CrossRef] [PubMed]

34. Yefimenko, N.; Portero-Tresserra, M.; Marti-Nicolovius, M.; Guillazo-Blanch, G.; Vale-Martinez, A. The AMPA receptor modulator S18986 in the prelimbic cortex enhances acquisition and retention of an odor-reward association. *Neuropharmacology* 2016, 102, 1437–1451. [CrossRef] [PubMed]

35. Cavazza, S.; Principato, G.; Chimirri, A.; Grassi, S.; Labrulé, V.; Sánchez-Prado, S.; et al. Reductases AKR1C1 and AKR1C3 Discovered by Virtual Screening of a Fragment Library. *J. Med. Chem.* 2009, 52, 77–86. [CrossRef]

36. Destot-Wong, K.D.; Liang, K.; Gupta, S.K.; Favrais, G.; Schwendimann, L.; Pansiot, J.; Baud, O.; Spedding, M.; Lelièvre, V.; Mani, S.; et al. The AMPA receptor positive allosteric modulator, S18986, is neuroprotective against neonatal excitotoxic and inflammatory brain damage through BDNF synthesis. *Neuropsychopharmacology* 2009, 34, 277–286. [CrossRef]

37. Yefimenko, N.; Portero-Tresserra, M.; Marti-Nicolovius, M.; Guillazo-Blanch, G.; Vale-Martinez, A. The AMPA receptor modulator S18986 in the prelimbic cortex enhances acquisition and retention of an odor-reward association. *Neurosci. Lett.* 2013, 548, 105–109. [CrossRef] [PubMed]

38. Malaquin, S.; Jida, M.; Courtin, J.; Lacombe, G.; Willand, N.; Deprez, B.; Deprez-Poulain, R. Water-based conditions for the microscale parallel synthesis of bicyclic lactams. *Tetrahedron Lett.* 2013, 54, 562–567. [CrossRef]

39. De Sarro, A.; De Sarro, G.; Chimirri, A.; Grassi, S.; Monforte, A.-M.; Zappala, M. Anticonvulsant activity of pyrrolo[1′,2′:1,2]imidazo[4,5-b]pyridines, pyrrolo[2′,1′:2,3]imidazol[4,5-c]pyridines and pyrrolo[2,1-f]purines in DBA/2 mice. *Gen. Pharmacol.* 1994, 25, 1027–1031. [CrossRef]

40. Cavazza, S.; Principato, G.; Chimirri, A.; Grassi, S.; Labrulé, V.; Sánchez-Prado, S.; et al. Separation of the enantiomers of anticonvulsant tricyclic pyrroloimidazolones by enanti-o-selective HPLC. A chiral recognition model and a chiroptical study. *Tetrahedron-Asymmetry* 1996, 7, 2577–2584. [CrossRef]

41. Chimirri, A.; Grassi, S.; Monforte, P.; Zappala, M.; Genchi, G. Pyrrolo[1′,2′:1,2]imidazo[4,5-b]pyridines, pyrrolo[2′,1′:2,3]imidazol[4,5-c]pyridines and pyrrolo[2,1-f]purines as potential benzodiazepine ligands. *Farmaco* 1993, 48, 1261–1269. [CrossRef]
42. Bergbreiter, D.E.; Osburn, P.L.; Frels, J.D. Mechanistic Studies of SCS-Pd Complexes Used in Heck Catalysis. *Adv. Synth. Catal.* 2005, 347, 172–184. [CrossRef]

43. Gorunova, O.N.; Novitskiy, I.M.; Grishin, Y.K.; Gloriozov, I.; Roznyatovsky, V.A.; Khrustalev, V.N.; Kochetkov, K.A.; Dunina, V.V. When Applying the Mercury Poisoning Test to Palladacycle-Catalyzed Reactions, One Should Not Consider the Common Misconception of Mercury(0) Selectivity. *Organometallics* 2018, 37, 2842–2858. [CrossRef]

44. Yu, K.; Sommer, W.; Richardson, J.M.; Weck, M.; Jones, C.W. Evidence that SCS Pincer Pd(II) Complexes are only Precatalysts in Heck Catalysis and the Implications for Catalyst Recovery and Reuse. *Adv. Synth. Catal.* 2005, 347, 161–171. [CrossRef]

45. Widegren, J.A.; Finke, R.G. A review of the problem of distinguishing true homogeneous catalysis from soluble or other metal-particle hetero-geneous catalysis under reducing conditions. *J. Mol. Catal. A Chem.* 2003, 198, 317–341. [CrossRef]

46. Phan, N.T.S.; Van Der Sluys, M.; Jones, C.W. On the Nature of the Active Species in Palladium Catalyzed Mizoroki–Heck and Suzuki–Miyaura Couplings–Homogeneous or Heterogeneous Catalysis, A Critical Review. *Adv. Synth. Catal.* 2006, 348, 609–679. [CrossRef]

47. Schmidt, A.F.; Kurokhtina, A.A. Distinguishing Between the Homogeneous and Heterogeneous Mechanisms of Catalysis in the Mizoroki-Heck and Suzuki-Miyaura Reactions: Problems and Prospects. *Kinet. Catal.* 2013, 53, 714–730. [CrossRef]

48. CrysAlisPro, Agilent Technologies, Version 1.171.37.31 (Release 14 January 2014 CrysAlis171.NET) (Compiled 14 January 2014, 18:38:05). Available online: https://www.agilent.com/cs/library/usermanuals/Public/CrysAlis_Pro_User_Manual.pdf (accessed on 10 January 2022).

49. Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. OLEX2: A complete structure solution, refinement and analysis program. *J. Appl. Cryst.* 2009, 42, 339–342. [CrossRef]

50. Sheldrick, G.M. A short history of SHELX. *Acta Crystallogr.* 2008, 64, 112–122. [CrossRef] [PubMed]

51. Macrae, C.F.; Bruno, I.J.; Chisholm, J.A.; Edgington, P.R.; McCabe, P.; Pidcock, E.; Rodriguez-Monge, L.; Taylor, R.; van de Streek, J.; Wood, P.A. Mercury CSD 2.0–New features for the visualization and investigation of crystal structures. *J. Appl. Cryst.* 2008, 41, 466–470. [CrossRef]

52. Spek, A.L. Single-crystal structure validation with the program PLATON. *J. Appl. Cryst.* 2003, 36, 7–13. [CrossRef]

53. Farrugia, L.J. WinGX suite for small-molecule single-crystal crystallography. *J. Appl. Cryst.* 1999, 32, 837–838. [CrossRef]

54. Aeberli, P.; Houlihan, W.J. Reaction of some oxo acids with anthranilic acid, anthranilamides, orthanilamides, and salicylamide. *J. Org. Chem.* 1968, 33, 2402–2407. [CrossRef]

55. Hadfield, J.A.; Pavlidis, V.H.; Rofey, J.R.A. Synthesis of Cytotoxic Pyrrrolo[1,2-a]-benzimidazol-1-ones. *Synth. Commun.* 1995, 25, 1319–1329. [CrossRef]