ArCH(OMe)$_2$ - a Pt$^{IV}$-catalyst originator for diverse annulation catalysis

Subhadeep Ghosh, Saikat Khamaru, Krishnanka S. Gayen & Dilip K. Maiti

Department of Chemistry, University of Calcutta, University College of Science, 92 A. P. C. Road, Kolkata-700009, India.

We discover an important property of a small molecule ArCH(OMe)$_2$, which transforms catalytically inactive Pt$^{II}$Br$_2$ procatalyst in situ to a powerful catalyst Pt$^{IV}$-species for diverse annulation reaction. The powerful catalytic system enables selective activation of C$_2$-H/N-H and C$_2$-H/C$_4$-H of acetoacetanilide and C=O/C=C of substituted butyne-1,2-dione for C-C/C-N, C-C/C-C and C-O/C-O bond-forming inter- and intramolecular annulation towards direct syntheses of functionalised 2-pyridones, cyclohexenones and 3(2H)-furanones respectively. In contrast to the common ligand, herein highly labile C-OMe bond of ArCH(OMe)$_2$ is expected to react with PtBr$_2$ towards generation of the high-valent active catalyst. Unlike catalyst promoter or initiator, the reaction does not occur with PtBr$_2$ in the absence of ArCH(OMe)$_2$. In situ generation of Pt$^{IV}$-species and -OMe fragment of ArCH(OMe)$_2$ were confirmed from the UV-vis characteristic peaks about 260 nm and trapping of -OMe group respectively. These observations provide new prospects and perspectives in catalysis for innovative catalyst design.
OSDD\(^{31}\), towards the easy access of these functionalised molecules through a simple, step-economical and cost-effective process, and these molecules will be developed as inexpensive drugs for millions of patients suffering from deadly malaria\(^{32}\) and tuberculosis\(^{33}\). After completion of a desired reaction, the Pt\(^{II}\)-procatalyst will be regenerated for the next cycle (eq. i) along with ArCH(OMe)\(_2\) equivalent aromatic aldehyde (5). The aldehyde may be converted to 4 through a simple acetal formation.

**Results**

1. **Development of the catalyst originator for the intermolecular annulation reaction.** We initiated the domino\(^{18–20}\) annulation reaction between N-(4-bromophenyl)-3-oxo-butyramide (1a: R\(^1\) = 4-BrC\(_6\)H\(_4\)) with 1,3-diphenylpropynone (2a: X = O; R\(^2\) = R\(^3\) = C\(_6\)H\(_5\)) in the presence of benzaldehyde dimethyl acetal (4a) and several transition metals (NiBr\(_2\), PdCl\(_2\), AuCl\(_3\), RuCl\(_3\) etc.) and rare-earth metals (La(OTf)\(_3\), CeCl\(_3\), Yb(OTf)\(_3\) etc.) as prospective procatalysts (entry 1, Table 1). Unfortunately, all attempts were unsuccessful, even under heating conditions. Compared to the widespread application of platinum compounds in catalysis\(^{34}\), PtBr\(_2\)-catalysed reactions are limited to only a few. For instance, this catalyst was utilised in the hydroamination of olefin\(^{35}\), in intramolecular enyne metathesis\(^{36}\) and in Markownikoff’s hydroarylation of terminal alkynes\(^{37}\). Gratifyingly, treatment of PtBr\(_2\) (3 mol%) at ambient temperature afforded the desired heterocycle 3-acetyl-1-(4-bromophenyl)-4,6-diphenyl-1\(^{H}\)-pyridin-2-one (6a) with moderate yield (60%, entry 2). PtBr\(_2\) is insoluble in acetonitrile solvent. Surprisingly, it dissolved in the reaction mixture on addition of PhCH(OMe)\(_2\) and transformed the colourless reaction mixture into the reddish brown solution. On the other hand, formation of even traces of desired product (6a) was not observed in the absence of the catalyst originator, which was confirmed by monitoring the reaction using TLC, HPLC and NMR spectroscopy. The reaction was optimised (entries 3–6) to improve the yield (86%), reaction rate (9 h) and procatalyst loading (2 mol%, entry 5).

### Table 1 | Optimisation of the intermolecular annulation reaction

| Entry | Catalyst (mol%) | Catalysis initiator (4) | Solvent, time (h) | Yield (%) |
|-------|-----------------|-------------------------|------------------|-----------|
| 1     | Other catalysts | PhCH(OMe)\(_2\) (4a)    | CH\(_2\)Cl\(_2\), 24 | -         |
| 2     | PtBr\(_2\) (3)  | PhCH(OMe)\(_2\) (4a)    | CH\(_2\)Cl\(_2\), 24 | 60        |
| 3     | PtBr\(_2\) (3)  | PhCH(OMe)\(_2\) (4a)    | MeCN, 8          | 87        |
| 4     | PtBr\(_2\) (3)  | PhCH(OMe)\(_2\) (4a)    | DMF, 24          | -         |
| 5     | PtBr\(_2\) (2)  | PhCH(OMe)\(_2\) (4a)    | MeCN, 9          | 86        |
| 6     | PtBr\(_2\) (1)  | PhCH(OMe)\(_2\) (4a)    | MeCN, 9          | 34        |
| 7     | PtBr\(_2\) (2)  | MgSO\(_4\) or Molecular sieve | MeCN, 24       | 82        |
| 8     | PtBr\(_2\) (2)  | 4-MeOC\(_6\)H\(_5\)CH(OMe)\(_2\) (4b) | MeCN, 9 | 50        |
| 9     | PtBr\(_2\) (2)  | 4-O2NC\(_6\)H\(_5\)CH(OMe)\(_2\) (4c) | MeCN, 9 | -         |
|10     | PtBr\(_2\) (2)  | HCH(OMe)\(_2\) (4d)    | MeCN, 24         | -         |
|11     | PtBr\(_2\) (2)  | Me\(_2\)C(OMe)\(_2\) (4e) | MeCN, 24        | -         |

![Figure 1](https://example.com/figure1.png)

**Figure 1** | Proposed intermolecular annulation strategy by suggested Pt\(^{IV}\)-active catalyst with ArCH(OMe)\(_2\).
Figure 2 | Bimolecular annulation process to 2-pyridones.
5). However, the role of PhCH(OMel) is not a desiccant for the reaction which was verified using activated magnesium sulfate and molecular sieve (entry 7). The aromatic dimethyl acetal (4) possessing an activated aromatic nucleus (4b, entry 8) provided a comparable yield (82%) whereas the deactivated one (4c, entry 9) drastically reduced the yield (50%). As expected, the reaction did not occur with aliphatic acetal and ketal without assistance from the aromatic ring (entries 10, 11) which is essential for breaking the C-O bond and stabilising the active Pt IV-catalyst.

2. N-C and C-C coupling to functionalized 2-pyridones. The reported synthesis of 2-pyridones includes multistep strategies, microwave and metathesis protocols, the one-pot Blaise reaction, direct synthesis involving the oxidative annulation of z,β-unsaturated amide and ketone, and our recently reported ring opening of chromone aldehydes with tandem cascade cyclisation. Substituted 2-pyridones are potential candidates for antihepatitis B, antitumor, human rhinovirus (HRV) 3C protease (3CP) inhibitor and noncompetitive antagonist related to epilepsy. We developed the direct construction of substituted 2-pyridone compounds (6a–k, Figure 2) from readily available chemicals acetoacetanilide (1) and 1,3-disubstituted propynone (2) at ambient temperature under neutral and benign reaction conditions. The substrate scope of this reaction revealed that the electron-donating substituent on the aryl group of acetoacetanilide derivatives significantly improved the reaction rate and yield relative to the precursor with an electron-withdrawing substituent (6g) or no substituent (6c and 6e). Aromatic and aliphatic substituents (6e) were tolerated in this highly regioselective bimolecular reaction. The annulation reaction was very selective to non-terminal precursor 2 as it was unsuccessful with terminal propynone precursors (2, R² = H). Exact mechanism of the reaction is unknown to us. Herein, Pt IV-active catalyst (II) is expected to bind with the triple bond (III) and carbonyl oxygen (IV) of 2 and subsequently N-C and C-C coupled cyclization (V–VII) with acetoacetanilide (1) in a cascade fashion led to removal of PhCHO (5a) and MeOH. The putative fused-intermediate VII immediately underwent reductive elimination to produce the desired heterocycle (6) along with the regenerated PtBr₂ procatalyst.

3. Dual C-C coupling to functionalized cyclohexenones. In recent studies, cyclohexenone compounds were utilised as versatile synths for the total synthesis of the antimalarial (+)-artemisinin, the antibiotic platencin, the important skeleton of the antimicrobial alkaloid (+)-2-oxo-agelasidine C and for biosynthetic intermediates. However, reports on synthesis of functionalised cyclohexenone are very limited. The selective activation of C₂-H and C₄-H

Figure 3 | Regioselective cascade annulation to cyclohexenones.
of acetoacetanilide derivatives and double C-C coupling with an appropriate propargyl moiety (eq. iii, Figure 1) led to the formation of functionalised cyclohexenone (7). However, this is a challenging task because C-C/C-N coupling is a more facile process (Figure 2) in the presence of a -NH- group. To overcome this challenge, we changed the precursor alkyne ketone (2) to its reduced form (3; Y = OH). We hypothesized that first C-C coupling (Figure 3) between 3 and 1 (C2-H) occurred with II by replacing the hydroxyl group of 3 (VIII) which expelled PhCHO (5a) and methanol. Second C-C bond formation (X) with CH3CO- group proceeded through formation of intermediate IX. The cyclic intermediate X subsequently underwent reductive elimination of the PtBr2 procatalyst with formation of the desired product 2-oxo-4-phenylcyclohex-3-enecarboxylic acid aryl amides (7).

Interestingly, the annulation reaction to compound 7 occurred under similar reaction conditions (entry 5, Table 1) and was very selective, and the corresponding N-C coupling 2-pyridones (6) were not observed in the post-reaction mixture. Herein, no product was observed using 1,3-disubstituted propargyl alcohol precursor (R3= Ph, VIII), which might be due to the considerable steric hindrance and/or electronic repulsion that appeared during reaction of propargyl alcohol (3) and acetoacetanilide with PtIV-active catalyst (II, Figure 1). The reaction was also very selective to non-terminal propargyl alcohol because the reaction was completely blocked when investigated using terminal alkynyl alcohols, such as propargyl alcohol.

### Discussion

We have demonstrated that aromatic aldehyde dimethyl acetal is a keen catalyst originator for transforming the catalytically inactive transition metal procatalyst PtBr2 to an active catalyst PtIV-species for both inter- and intramolecular annulation to several valuable heterocycles and carbocycles. Organic ligands greatly influence the catalytic activity of metallic compounds. The annulation reaction was examined using different bidentate ligands and conventional additives, such as ethylene glycol dimethyl ether, dimethyl tartarate, 1,2-diphenyl ethylene glycol, catechol, DPPE, COD, α-pinene, norbornadiene, etc., and all attempts were unsuccessful to provide compound 6. These observations strongly supported that the role of ArCH(OMe)2 was not simple as a conventional ligand in the remarkable catalysis.

**Figure 4** Synthesis of 3(2H)-furanone with trapping of the OMe group.

4. **Dual C-O coupling to substituted 3(2H)-furanones.** The 3(2H)-furanone (8) compound is a human tyrosinase inhibitor, the aroma component of soy sauce and is used as a valuable synthon for the total synthesis of the renal cancer cell lines inhibitor (−)-Englerin A. The widespread application of the heterocyclic scaffold and the availability of only a few synthetic methods in the literature prompted us to establish an easy synthetic method. Gratifyingly, double O-C coupling intramolecular cyclization of non-terminal butyne-1,2-dione (5) with the PhCH(OMe)2 was observed under the similar reaction conditions to afford 3(2H)-furanone (8, Figure 4). In fact, this developed method is the second approach for the direct synthesis of 2-alkoxy-3(2H)-furanones following the AuCl3-catalysed annulation of 3-oxo-butyne analogues reported by Liu and coworkers. From a synthetic perspective, this reaction is straightforward, high yielding (85–95%), tolerant to double bonds (8d) and aromatic rings, and can also directly synthesise a complex compound bearing three heterocycles (8e). It is proposed that the intramolecular cyclisation occurred involving formation of C=O and triple bond-coordinated PtIV-activated intermediate XI which subsequently transformed to 8 by the migration of -OMe, as well as the formation of O-C bond involving the conversion of C=O to C–C. Interestingly, the PtIV-species was so selective for binding to precursor 5 that even in presence of acetoacetanilide (1), it did not form the corresponding 2-pyridone (6) by annulation with the R2– C= C– CO- moiety (Figure 2).
approach. To the best of our knowledge, there is no such example in the literature of using a catalyst originator to a procatalyst that displays outstanding catalytic activity. To understand the involvement of PtIV-species in this process, reactions were performed separately with PtIV-compounds such as PtCl₄, H₂PtCl₆, PtCl₄-4a and H₂PtCl₆-4a. Unfortunately, the formation of the desired product (6a) was not observed in these reaction mixtures. UV-vis spectroscopic analyses of PtBr₂ and PhCH(OOMe)₂ in acetonitrile and also the reaction mixture (entry 5, Table 1) revealed the presence of PtIV-species through the characteristic absorbance band that appeared at 259.84 and 260.02 nm respectively (supplementary information). These observations clearly indicated that only 4a-modified PtIV was the active catalyst for the robust annulation processes. The formation of PhCHO (5a) was observed due to reaction of catalyst originator PhCH(OOMe)₂ and in situ generated water during the course of the annulation process. Compound 5a was isolated from the post-reaction mixture and characterized. The formation of MeO-/MeOH was also verified by trapping it in an intramolecular cyclisation of disubstituted but-3-yne-1,2-diketone (5) to afford 2-methoxy-3(2H)-furanone derivative (8, Figure 4). Interestingly, the activated PtIV-species was so selective for binding to precursor 3 (Figure 3) and 5 (Figure 4) that even in presence of acetocetanilide (1), it did not form the corresponding 2-pyridone (6). This inexpensive and readily available organic catalyst originator installed novel catalytic power to procatalyst PtBr₂ for activation of C-H, N-H, C-O and π-bonds towards selective C-C/C-N, C/C/C-C and C-O/C-O coupled annulation to achieve the direct synthesis of ubiquitous carboxylics and heterocycles. The robust synthetic protocol was developed under benign and neutral reaction conditions to obtain highly functionalised 2-pyridones (6), cyclohexenones (7) and 3(2H)-furanones (8) in excellent yield and with very low catalytic loading using the common laboratory reagent acetocetanilide, non-halogenated precursor α-ketoaldehydes and propargyl alcohol, and environmentally safe water was generated as a byproduct (Figure 5). The transformation of the catalyst originator to its corresponding aldehyde, trapping of the fragmentated –OMe group and the in situ generation of the PtIV-active catalyst were experimentally confirmed. We anticipate that this new concept in catalysis will find immense application in synthetic organic chemistry towards innovative catalyst design, the development of new catalyst originator, procatalysts, and novel reactions; and the newly designed catalysts will dominate as a work-horse in the facile synthesis of novel functional molecules with high synthetic efficiency.

**Methods**

A solution of β-ketoanilide (1, 1.0 mmol), benzaldehyde dimethyl acetal (4a, 152 mg, 1.0 mmol) and 1,3-disubstituted 1-propynyl (2, 1.0 mmol) in acetonitrile (10 mL) was stirred at 0°C. Platinum (II) bromide (7 mg, 0.026 mmol) was added, and the mixture was stirred at ambient temperature. The progress of the reaction was monitored by TLC, and the reaction was complete within ≤5–25 h depending on the use of the substrates. The post-reaction mixture was concentrated in a rotary evaporator under reduced pressure at room temperature and the residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with distilled water (3 × 10 mL), dried over activated sodium sulphate and concentrated in a rotary evaporator. Thus, the reaction with N-(4-bromophenyl)-3-oxo-butyramide (1a, 256 mg, 1.0 mmol) and 1,3-diphenylpropynone (2a, 206 mg, 1.0 mmol) afforded 3-acetyl-1-(4-bromophenyl)-4,6-diphenyl-1H-pyridin-2-one (6a) in an yield of 86% (380 mg, 0.86 mmol) after purification by column chromatography on basic alumina (100–200 mesh) with 8% ethyl acetate in hexane as an eluent. All of the new 2-pyridone compounds (6a–k) were characterised using NMR (1H, 13C and DEPT), FT-IR and mass (HR-MS) spectroscopic measurements and single crystal XRD analyses. Functionalised cyclohexenones (7) and 2-methoxy-3(2H)-furanones (8) were also synthesized under similar reaction conditions and fully characterised (supplementary information). The structures of all the new compounds (6–8) were elucidated by performing NMR, FT-IR and ESI-MS spectroscopic measurements and single crystal XRD-analyses of 6k, 7g and 8f.

1. Rothenberg, G. Catalysis (Wiley/VHC, Weinheim, 2008).
2. Berzelius, J. J. Årsberättelsen om framsteg i fysik och kemi. Royal Swedish Academy of Sciences (1835).
3. Peplow, M. Catalysis: The accelerator. Nature 495, S10–S11 (2013).
4. Davies, H. M. L. & Manning, I. R. Catalytic C-H functionalization by metal carbenoid and nitrenoid insertion. Nature 451, 417–424 (2008).
5. Hartwig, J. F. Carbon-heteroatom bond formation catalysed by organometallic complexes. Nature 455, 314–322 (2008).
6. Dong, G., Teo, P., Wickens, Z. K. & Grubbs, R. H. Primary alcohols from terminal olefins: formal anti-Markovnikov hydration via triple relay catalysis. Science 333, 1609–1612 (2011).
7. Sengupta, T., Gayen, K. S., Pandit, P. & Maiti, D. K. FeCl₃-catalyzed hydrogenation of 1,3-hexadiene over a Pd/silica catalysts promoter and poison. Langmuir 16, 6519–6526 (2000).
10. Campos, K. R. et al. Controlled semihydrogenation of aminoaalkynes using ethylenediamine as a poison of Lindlar’s catalyst. J. Org. Chem. 66, 3634–3635 (2001).
11. Dronavajjala, K. D. et al. A simple technique to grow polymer brushes using in situ surface ligation of an organometallic initiator. J. Am. Chem. Soc. 128, 13040–13041 (2006).
12. Xiaoefi, L., Haoji, X., Guining, L. & Minhua, Z. Investigation of Cu-based catalyst for direct synthesis of ethyl acetate from ethane: improvement of thermal stability of Cu–Cr–Zr composite oxide catalyst by addition of Mn promoter. Ind. Eng. Chem. Res. 51, 8974–8978 (2012).
13. Dondoni, A. & Massi, A. Design and synthesis of new classes of heterocyclic C-glycoconjugates and carbon-linked sugar and heterocyclic amino acids by asymmetric multicomponent reactions (AMCRs). Acc. Chem. Res. 39, 451–463 (2006).
14. Ma, S. Handbook of Cyclization Reactions, (Wiley-VHC, 2009).
15. Rittleng, V., Sirlin, C. & Pfeffer, M. Ru-, Rh-, and Pd-catalyzed C-C bond formation involving C-H activation and addition on unsaturated substrates: reactions and mechanistic aspects. Chem. Rev. 102, 1731–1769 (2002).
16. Saima, Y., Khamurai, S., Gayen, K. S., Pandit, P. & Maiti, D. K. Efficient catalytical cyclizations of three and two imine assemblies: direct access to tetralyldimido[1,5]-imidazol-7-one and imidazoles. Chem. Commun. 48, 6601–6603 (2012).
17. Arocchiam, P. B., Bruneau, C. & Dinxneuf, P. H. Ruthenium(II)-catalyzed C-H bond activation and functionalization. Chem. Rev. 112, 5879–5918 (2012).
18. Tietze, L. F., Brasche, G. & Gercke, K. Domino reactions in organic synthesis (Wiley-VCH. Weinheim, Germany, 2006).
19. Dhar, D. et al. CeCl 3\[THO\] catalyzed C-C and C-N bond-forming cascade cyclization with subsequent side-chain functionalization and rearrangement: A domino approach to pentasubstituted pyroles analogues. J. Org. Chem. 77, 10441–10449 (2012).
20. Pellissier, H. Stereocomponted domino reactions. Chem. Rev. 113, 442–524 (2013).
21. Zhang, Z., Zhang, Q., Yan, Z. & Liu, Q. One-step synthesis of the tricyclic core of martincilic acid from 2-(cyanomethyl)-3-oxo-N-arylbutanamides. J. Org. Chem. 72, 9808–9810 (2007).
22. Wei, Y. et al. Acetocetanilides as masked isocyanates: facile and efficient synthesis of unsymmetrically substituted amines. Org. Lett. 12, 4220–4223 (2010).
23. Hali, L. M. et al. Late stage oxidations during the biosynthesis of the 2-pyridone tenellin in the entomopathogenic fungus Beauveria bassiana. J. Am. Chem. Soc. 130, 17988–17996 (2008).
24. Peng, X. et al. Cerebroside and 2-pyridone alkaloids from the halotolerant fungus Penicillium chrysogenum grown in a hypersaline Medium. J. Nat. Prod. 74, 1298–1302 (2011).
25. Kumarabhampy, M. et al. Antiprotozoal and antimicrobial compounds from the plant pathogen septoria piracarum. J. Nat. Prod. 75, 883–889 (2012).
26. Panthama, N., Kanokmedhakul, S., Kanokmedhakul, K. & Sotyong, K. Cytotoxic and antimalarial azaphilones from chaetomium longirostre. J. Nat. Prod. 74, 2395–2399 (2011).
27. Yang, F. et al. Antimicrobial metabolites from the Paracel Islands sponge aegla mauritiana. J. Nat. Prod. 75, 774–778 (2012).
28. Long, C. et al. Proteasome inhibitors from neoboutonia melleri. J. Nat. Prod. 75, 34–47 (2012).
29. Taylor, S. L., Peterson, R. E. & Gray, L. E. Isolation of gregatin A from phialophora et al. J. Org. Chem. 74, 892–897 (2009).
30. Xu, Z. et al. Design, synthesis, and antiparasitic B virus activities of novel 2-pyridone derivatives. J. Med. Chem. 53, 660–668 (2010).
31. Zhu, C. & Cook, S. P. A concise synthesis of (+)-Artemisinin. J. Am. Chem. Soc. 134, 13577–13579 (2012).
32. Yoshimitsu, T., Nojima, S., Hashimoto, M. & Tanaka, T. Total synthesis of (+)-Platencin. Org. Lett. 13, 3698–3701 (2011).
33. Yang, F. et al. Antimicrobial metabolites from the paracel islands sponge aegla mauritiana. J. Nat. Prod. 75, 774–778 (2012).
34. McGlinchey, R. P., Nett, M. & Moore, B. S. Unraveling the biosynthesis of the sporulide cyclohexene building block. J. Am. Chem. Soc. 130, 2406–2407 (2008).
35. Bolze, P., Dickmeiss, G. & Jørgensen, K. A. Organocatalytic asymmetric synthesis of 5-tritylalkylidylylcyclohex-2-ones and the transformation into useful building blocks. Org. Lett. 10, 3753–3756 (2008).
36. Inokoishi, Y., Sasakura, N., Nakano, K., Ichikawa, Y. & Kotsuki, H. A new powerful strategy for the organocatalytic asymmetric construction of a quaternary carbon stereogenic center. Org. Lett. 12, 1616–1619 (2010).
37. Okombi, S., Rival, D., Bonnet, S., Mariotte, A.-M., Perrier, E. & Boumendjl, A. Discovery of benzylidenenbenzofuran-3(2H)-one (aurones) as inhibitors of tyrosinase derived from human melanocytes. J. Med. Chem. 49, 329–333 (2006).
38. Steinhaus, P. & Schiebere, P. Characterization of the key aroma compounds in soy sauce using approaches of molecular sensory science. J. Agric. Food Chem. 55, 6262–6269 (2007).
39. Li, Z., Nakashige, M. & Chain, W. J. A brief synthesis of (+)-Englerin. J. Am. Chem. Soc. 133, 6553–6556 (2011).
40. Liu, Y. et al. Gold-catalyzed highly efficient access to 3(2H)-furanones from 2-oxo-3-butanoylates and related compounds. Org. Lett. 8, 3445–3448 (2006).
41. Georgieva, M. & Andonovski, B. Determination of platinum(IV) by UV spectrophotometry. Anal. Bioanal. Chem. 375, 836–839 (2003).