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Catalytic Anti-Markovnikov Transformations of Hindered Terminal Alkenes Enabled by Aldehyde-Selective Wacker-Type Oxidation

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Supporting Information

ABSTRACT: A new strategy for the functionalization of sterically hindered terminal olefins is reported. Alkenes bearing quaternary carbons at the allylic or homoallylic position are readily oxidized to the corresponding aldehydes by palladium/copper/nitrite catalysis. A broad range of functional groups including esters, nitriles, silyl ethers, vinylogous esters, ketones, lactones, and β-ketoesters are tolerated under the reaction conditions. The crude aldehyde products can be transformed further, enabling direct conversion of hindered terminal alkenes to various other synthetically useful functional groups, resulting in formal anti-Markovnikov hydroamination, among other transformations.

The oxidation of terminal olefins to carbonyls, known as the Tsuji–Wacker process, has proven to be a powerful tool in synthetic chemistry since its discovery.[1] Formally, the Wacker reaction is among the oldest known methods for C–H oxidation. The synthetic utility of the Tsuji–Wacker oxidation stems from its efficiency and broad functional group compatibility, and modifications to the original conditions have further expanded its applications.[2−4] One such modification employs $AgNO_2$ as a cocatalyst with $PdCl_2(PhCN)_2$ and $CuCl_2{\cdot}2H_2O$ in 15:1 *t*-BuOH/$MeNO_2$ to reverse the regioselectivity, enabling selective conversion of unbiased terminal alkenes to aldehydes in high yields instead of the traditionally favored methyl ketone products (Figure 1A).[5]

Despite the robustness of the nitrite-modified Tsuji–Wacker reaction, limitations remain. Specifically, oxidation of substrates bearing proximal steric hindrance such as quaternary carbons, common intermediates in complex molecule synthesis, has yet to be demonstrated. Our group has developed various strategies for the construction of quaternary stereocenters, most notably by catalytic enantioselective decarboxylative allylic alkylation.[6] While these methods have been employed to great effect in total synthesis,[7] the allylic alkylation products are also unique substrates for methodological studies (Figure 1B). For instance, we have recently shown that these sterically hindered compounds do not react as desired under various conditions for allylic oxidation, requiring further methods development for success.[8]

Examples of sterically encumbered substrates are often absent from methodology reports, impeding their utility in complex molecule synthesis. Indeed, the oxidation of hindered terminal alkenes to the corresponding aldehydes is often

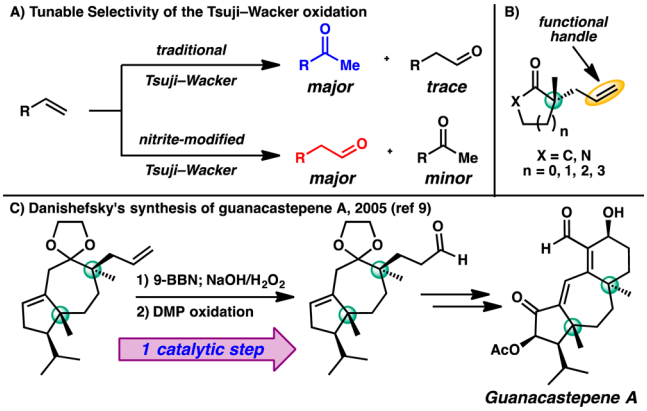

Figure 1. (A) Tsuji–Wacker selectivity. (B) Typical products of enantioselective decarboxylative allylic alkylations. (C) Common strategy for preparation of hindered aldehydes.

accomplished in two stoichiometric steps: hydroboration–oxidation, followed by Dess–Martin or Swern oxidation (Figure 1C).[9] However, with the modern capabilities of the nitrite-modified Tsuji–Wacker reaction, we hypothesized this sequence could be achieved in one catalytic step, thereby streamlining synthetic strategy and generating less waste compared to the stoichiometric processes. To the best of our knowledge, the research disclosed in this report represents the first general examples of the selective oxidation of sterically hindered olefins directly to aldehydes.

We began our investigations by examining the effect of different nitrite sources on the reactivity of malonate derivative **1a** (Figure 2). Although various nitrite sources gave comparable yields of desired aldehyde **2a** (Entries 2–7), we found that $AgNO_2$ gave the optimal overall yield and selectivity for this hindered system (Entry 8). The exclusion of any nitrite source severely impeded oxidation (Entry 1), corroborating theories concerning the critical role nitrite plays in this transformation.[5,10]

Having elucidated the optimized reaction conditions, we explored the reactivity of various substrates bearing proximal quaternary carbons (Table 1). We were delighted to find that substrates containing ester and nitrile functionalities readily underwent oxidation, generating the corresponding aldehydes in excellent yields (Entries 1–3). Although alcohols were incompatible with the reaction conditions, TBS-ether **1d** was a

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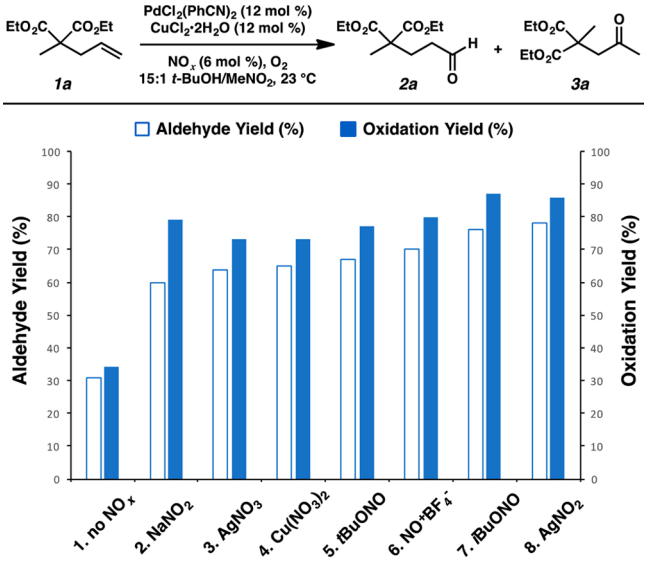


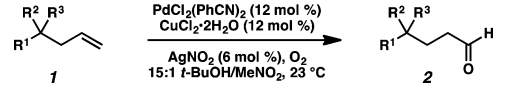
Figure 2. Catalyst optimization. Experiments were conducted on 0.2 mmol of **1a** at 0.05 M over 14 h. Oxidation yield is the sum of the yields of **2a** and **3a**.

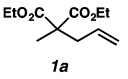
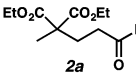
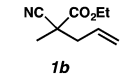
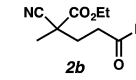
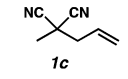
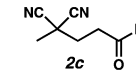
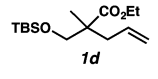
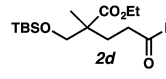
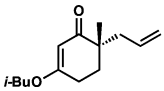
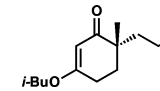
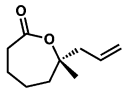
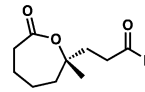
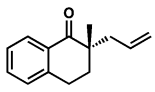
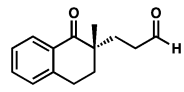
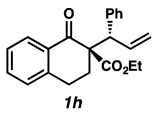
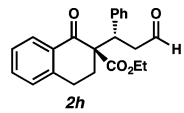
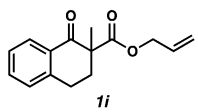
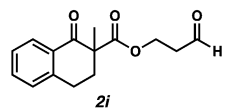
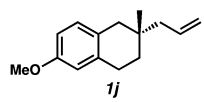
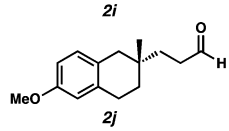
competent substrate, furnishing aldehyde **2d** in high yield (Entry 4). Vinylogous ester **1e**, caprolactone derivative **1f**, and tetralone-derived substrates **1g**–**1i** also performed well in the reaction (Entries 5–9). Notably, deoxytetralone derivative **1j** was also a suitable substrate, demonstrating that oxidation can occur in the absence of an adjacent carbonyl functionality (Entry 10). Remarkably, oxidation of compounds bearing allylic quaternary carbons also proceeded (Table 2). For instance, α-vinylic ketone **4a** was oxidized to aldehyde **5a** in high yield (Entry 1). Bulkier substitution at the allylic position was also tolerated, with α-vinylic ester **4b** reacting smoothly to generate aldehyde **5b** in good yield (Entry 2). Gratifyingly, oxidation of complex organic molecules was also possible, as conversion of aspewentin B derivative **4c**[11] to aldehyde **5c** proceeded in moderate yield (Entry 3).

Inspired by the robustness of this transformation on such sterically burdened substrates, we sought to expand the synthetic impact of the nitrite-modified Tsuji–Wacker reaction by leveraging the reactivity of the aldehyde products. Specifically, we envisioned that subsequent reductive amination could effect formal anti-Markovnikov hydroamination of the olefin substrate.

The addition of amines to alkenes has been recognized as an important research topic due to the ubiquity of amines in biologically active small molecules.[12,13] Anti-Markovnikov hydroamination remains of particular interest because Markovnikov addition is usually favored. Regrettably, many current strategies toward this challenging transformation require biased substrates, expensive or commercially unavailable catalysts and reagents, rigorously air-free conditions, strong bases, or high temperatures to achieve regioselective hydroamination.[14] Furthermore, in some cases product scope is restricted to tertiary amines,[14d–f] and in other cases the reaction conditions are highly reducing.[14g] Noting these limitations, we anticipated that reductive amination of the aldehyde generated from the anti-Markovnikov Tsuji–Wacker oxidation could provide a mild and efficient alternative approach to this important synthetic transformation.

Table 1. Substrate Scope of the Aldehyde-Selective Tsuji–Wacker Oxidation on Hindered Alkenes



Entry	Alkene Substrate	Aldehyde Product	Yield
1	 1a	 2a	90%[b]
2	 1b	 2b	81%
3	 1c	 2c	89%
4	 1d	 2d	87%
5	 1e	 2e	60%[d,f]
6	 1f	 2f	67%[c]
7	 1g	 2g	80%[c]
8	 1h	 2h	75%[b,e,g]
9	 1i	 2i	74%[c]
10	 1j	 2j	63%[c]

[a]Reactions performed on 0.2 mmol of **1** at 0.05 M over 7–17 h. Isolated yields. [b]Methyl ketone observed, 91–96% aldehyde selectivity. [c]Enal observed, 80–97% aldehyde selectivity. [d]Enal observed, 67% aldehyde selectivity. [e]Reaction time = 40 h. [f]Conducted on 0.08 mmol of **1e**. [g]Conducted on 0.06 mmol of **1h**.

We selected alkene **1a** as the substrate for our formal hydroamination studies due to its excellent performance in the nitrite-modified Tsuji–Wacker oxidation. Upon full conversion of the olefin under aldehyde-selective Tsuji–Wacker conditions, filtration through a pad of silica and subsequent treatment of the residue with amine and $NaBH(OAc)_3$ at ambient temperature in DCE afforded the reductive amination products smoothly (Table 3). Aliphatic (**6aa**–**6ac**) and aromatic (**6ad**) tertiary amines were prepared in excellent yields (Entries 1–4), and both electron-rich (**6ae**) and electron-poor (**6af**) anilines were also obtained in high yields (Entries 5 and 6). Notably, both tertiary and secondary amines are accessible through this operationally simple sequence.

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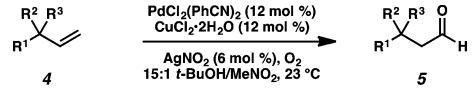
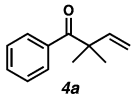
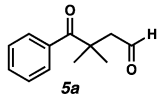
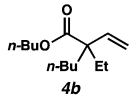
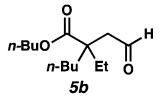
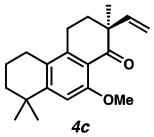
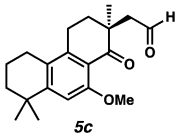
Table 2. Aldehyde-Selective Tsuji–Wacker Oxidation of Allylic Quaternary Alkenes

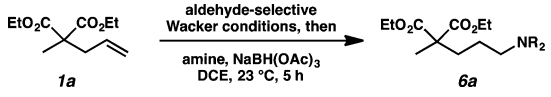


4 5

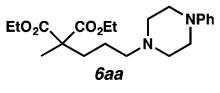
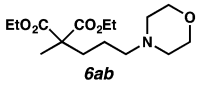
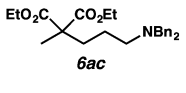
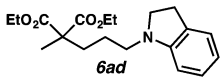
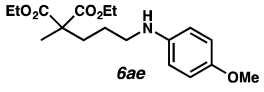
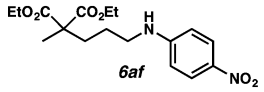
Entry	Alkene Substrate	Aldehyde Product	Yield
1	 4a	 5a	85%[b]
2	 4b	 5b	69%[b]
3	 4c	 5c	64%[c]

[a]Reactions performed on 0.2 mmol of **4** at 0.05 M over 20–48 h. Isolated yields. [b]Methyl ketone observed, 88–91% aldehyde selectivity. [c]Conducted on 0.07 mmol of **4c**.

Table 3. Formal Anti-Markovnikov Hydroamination



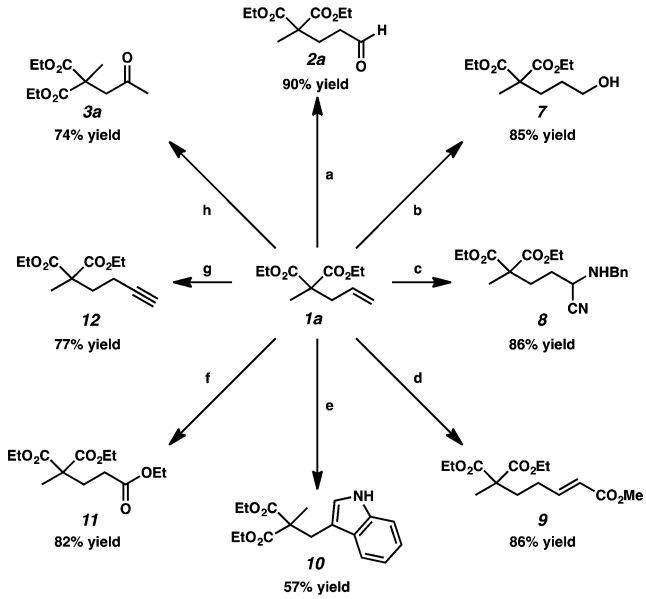
1a 6a

Entry	Amine	Product	Yield
1	*N*-phenylpiperazine	 6aa	98%
2	morpholine	 6ab	91%
3	dibenzylamine	 6ac	76%
4	indoline	 6ad	96%
5	4-methoxyaniline	 6ae	86%
6	4-nitroaniline	 6af	95%

[a]Reactions performed on 0.2 mmol of **1a**. Isolated yields. Conditions for nitrite-Wacker: $PdCl_2(PhCN)_2$ (0.12 equiv), $CuCl_2·2H_2O$ (0.12 equiv), $AgNO_2$ (0.06 equiv), 15:1 *t*-BuOH/$MeNO_2$ (0.05 M), 23 °C, 12 h.

Encouraged by the success of the formal hydroamination reactions, we sought to extend our two-step procedure to other synthetically applicable transformations, enabling conversion of the alkene starting material to a variety of functional groups. For instance, sodium borohydride reduction of the crude aldehyde afforded formal anti-Markovnikov hydration product **7** in good yield (Scheme 1). Likewise, Strecker conditions

Scheme 1. Synthetic Transformations of Alkene 1a



[a]Reactions conducted on 0.2 mmol of **1a**. Isolated yields. For nitrite-Wacker conditions, see Table 3. (a) nitrite-Wacker; (b) nitrite-Wacker then $NaBH_4$, 1:1 $MeOH/CH_2Cl_2$, 0 → 23 °C; (c) nitrite-Wacker then $BnNH_2$, TMSCN, THF, 23 °C; (d) nitrite-Wacker then $Ph_3P{=}CHCO_2Me$, THF, 0 → 23 °C; (e) nitrite-Wacker then $PhNHNH_2·HCl$, 4% aq. H_2SO_4, EtOH, 110 °C; f) nitrite-Wacker then $Pd(OAc)_2$, XPhos, K_2CO_3, acetone, EtOH, 23 °C; g) nitrite-Wacker then Ohira–Bestmann reagent, EtOH, 60 °C; h) $PdCl_2$, $CuCl_2·2H_2O$, NaCl, 0.2 M HCl, DMF, O_2, 35 → 60 °C.

allowed access to α-aminonitrile **8**, and Horner–Wadsworth–Emmons olefination furnished α,β-unsaturated methyl ester **9** in high yield, effecting a two-carbon homologation of alkene **1a**. Fischer indolization also proved successful, affording 3-substituted indole **10** in moderate yield. Further oxidation[15] of the crude aldehyde delivered tris-ethyl ester **11** in high yield whereas treatment with the Ohira–Bestmann reagent enabled conversion of the terminal alkene to a terminal alkyne of one-carbon chain length longer (**12**). Finally, the reactivity of alkene **1a** under traditional Tsuji–Wacker conditions was assessed, providing methyl ketone **3a** in good yield.

In summary, we have amplified the synthetic impact of the aldehyde-selective Tsuji–Wacker oxidation by demonstrating its efficacy on diversely functionalized terminal alkenes bearing sterically demanding quaternary carbons at the allylic or homoallylic position, common motifs among intermediates in complex molecule synthesis. Moreover, we have illustrated how the aldehyde products of these reactions can be further transformed, enabling direct conversion of the alkene functional handle to a variety of other functional groups. We anticipate that this operationally simple methodology will find many applications in chemical synthesis since several of these overall transformations are unprecedented or require multiple steps. Further investigations into the utility of this methodology are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and compound characterization (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Smidt, J.; Hafner, W.; Jira, R.; Sedlmeier, J.; Sieber, R.; Kojer, H.; Rüttinger, R. *Angew. Chem.* **1959**, *71*, 176−182. (b) Tsuji, J. *Synthesis* **1984**, *1984*, 369−384. (c) Takacs, J. M.; Jiang, X.-T. *Curr. Org. Chem.* **2003**, *7*, 369−396. (d) Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*, 2nd ed.; Wiley: Hoboken, NJ, 2004. (e) Jira, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9034−9037.

(2) (a) Mitsudome, T.; Mizumoto, K.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 1238−1240. (b) Morandi, B.; Wickens, Z. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 2944−2948. (c) DeLuca, R. J.; Edwards, J. L.; Steffens, L. D.; Michel, B. W.; Qiao, X.; Zhu, C.; Cook, S. P.; Sigman, M. S. *J. Org. Chem.* **2013**, *78*, 1682−1686.

(3) (a) Mitsudome, T.; Umetani, T.; Nosaka, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 481−485. (b) Cornell, C. N.; Sigman, M. S. *Inorg. Chem.* **2007**, *46*, 1903−1909. (c) Gligorich, K. M.; Sigman, M. S. *Chem. Commun.* **2009**, 3854−3867. (d) Campbell, A. N.; Stahl, S. S. *Acc. Chem. Res.* **2012**, *45*, 851−863.

(4) (a) Michel, B. W.; Camelio, A. M.; Cornell, C. N.; Sigman, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 6076−6077. (b) Michel, B. W.; McCombs, J. R.; Winkler, A.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 7312−7315. (c) Sigman, M. S.; Werner, E. W. *Acc. Chem. Res.* **2012**, *45*, 874−884.

(5) (a) Wickens, Z. K.; Morandi, B.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 11257−11260. (b) Wickens, Z. K.; Skakuj, K.; Morandi, B.; Grubbs, R. H. *J. Am. Chem. Soc.* **2014**, *136*, 890−893. For a recently reported alternative, see: Ning, X.-S.; Wang, M.-M.; Yao, C.-Z.; Chen, X.-M.; Kang, Y.-B. *Org. Lett.* **2016**, *18*, 2700−2703.

(6) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044−15045. For a review on enantioselective formation of quaternary stereocenters, see: Liu, Y.; Han, S.-J.; Liu, W.-B.; Stoltz, B. M. *Acc. Chem. Res.* **2015**, *48*, 740−751.

(7) For reviews on the use of enantioselective decarboxylative allylic alkylations in total synthesis, see: Hong, A. Y.; Stoltz, B. M. *Eur. J. Org. Chem.* **2013**, *2013*, 2745−2759.

(8) Xing, X.; O'Connor, N. R.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2015**, *54*, 11186−11190.

(9) For an example of this strategy, see: Mandal, M.; Yun, H.; Dudley, G. B.; Lin, S.; Tan, D. S.; Danishefsky, S. J. *J. Org. Chem.* **2005**, *70*, 10619−10637.

(10) (a) Jiang, Y.-Y.; Zhang, Q.; Yu, H.-Z.; Fu, Y. *ACS Catal.* **2015**, *5*, 1414−1423. (b) Keith, J. A.; Nielsen, R. J.; Oxgaard, J.; Goddard, W. A., III *J. Am. Chem. Soc.* **2007**, *129*, 12342−12343.

(11) Liu, Y.; Virgil, S. C.; Grubbs, R. H.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2015**, *54*, 11800−11803.

(12) For a general review on hydroamination, see: (a) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795−3892.

(13) (a) Henkel, T.; Brunne, R. M.; Müller, H.; Reichel, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 643−647. (b) Hili, R.; Yudin, A. K. *Nat. Chem. Biol.* **2006**, *2*, 284−287.

(14) For selected examples, see: (a) Ryu, J.-S.; Li, G. Y.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 12584−12605. (b) Crimmin, M. R.; Casely, I. J.; Hill, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 2042−2043. (c) Bronner, S. M.; Grubbs, R. H. *Chem. Sci.* **2014**, *5*, 101−106. (d) Utsunomiya, M.; Kuwano, R.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 5608−5609. (e) Rucker, R. P.; Whittaker, A. M.; Dang, H.; Lalic, G. *J. Am. Chem. Soc.* **2012**, *134*, 6571−6574. (f) Zhu, S.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 15746−15749. (g) Strom, A. E.; Hartwig, J. F. *J. Org. Chem.* **2013**, *78*, 8909−8914.

(15) Tschaen, B. A.; Schmink, J. R.; Molander, G. A. *Org. Lett.* **2013**, *15*, 500−503.

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