View Article Online View Journal



Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: C. Qiu, K. Yao, X. Zhang and H. Gong, *Org. Biomol. Chem.*, 2016, DOI: 10.1039/C6OB02269C.



This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the **author guidelines**.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard <u>Terms & Conditions</u> and the ethical guidelines, outlined in our <u>author and reviewer resource centre</u>, still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.



rsc.li/obc

Journal Name



Ni-Catalyzed Reductive Coupling of α -Halocarbonyl Derivatives with Vinyl Bromides

Canbin Qiu,^a Ken Yao^{a,*} Xinhua Zhang^{b,*} and Hegui Gong^{a,*}

Received 00th January 20xx, Accepted 00th January 20xx DOI: 10.1039/x0xx00000x

www.rsc.org/

Published on 15 November 2016. Downloaded by Athabasca University on 16/11/2016 01:30:33.

This work describes vinylation of α -halo carbonyl compounds with vinyl bromides under Ni-catalyzed reductive coupling conditions. While aryl-conjugated vinyl bromides entails pyridine as the sole labile ligand, the alkyl-substituted vinyl bromides requires both bipyridine and pyridine as the co-ligands.

Carbonyl compounds bearing α -vinyl groups are important organic synthons and some are bioactive.¹⁻² They are generally prepared via transition metal-catalyzed α -alkenylation of carbonyl compounds.³⁻⁵ In this context, Pd and Ni-catalyzed vinylation of enolates with vinyl electrophiles has received much attention.³⁻⁴ The oxidative coupling of enolates with vinyl-boron reagents should also be noted.⁵ On the other hand, the Ni- and Pd-catalyzed coupling of vinyl- metallic reagents with α -halocarbonyl compounds represents a different strategy, wherein asymmetric methods have also been achieved (Scheme 1).⁶

In contrast, the construction of the vinyl-alkyl C-C bonds from unactivated alkyl halides with vinyl halides has been explored using Ni-, Pd- as well as photo-redox/Ni-catalyzed reductive protocols,⁷⁻¹⁰ wherein excellent chemoselectivity featuring equimolar loading of the coupling partners has been succeeded using Ni/bipy-catalytic conditions.^{7b} However, vinylation of α-carbonyl compounds has only been disclosed using an electrochemical reductive coupling method,¹¹ although the equivalent arylation methods have been dislosed.¹²⁻¹³ Therefore, development of parallel chemical reductive conditions is needed for practical reasons. Noteworthy is that the activated alkyl halides such as α -halocarbonyl derivatives generally display distinct reactivity from the unactivated counterparts. Dimerization and hydrodehalogenation side reactions may become problematic for substrates of these types.¹⁴⁻¹⁵ Hence, exploration of reductive coupling methods based on α-halocarbonyl derivatives is nontrivial.

Herein, we demonstrate that preparation of 3-enoates and 3enamides can be readily accomplished from cross-electrophile coupling of the vinyl and a-halo carbonyl derivatives (Scheme 1). For aryl-conjugated vinyl halides, pyridine was used as the sole ligand, whereas for alkyl-decorated vinyl halides, co-existence of pyridine and bipyridine was necessary for the vinylation process.

Scheme 1. Vinylation of α -carbonyl compounds



We have determined that the reaction of ethyl 2chloropropanoate **1a** with (2-bromovinyl)benzene **2** (E/Z = 84/16) afforded 3 in an optimal yield of 88% with an E/Z ratio of 90:10, wherein 1 equiv of pyridine was the only labile ligand (Table 1, entry 1).¹⁶ The addition of 2,2'-bipyridine (30 mol %) eroded the reaction yield to 70%, which is pivotal for the analogous electrochemical method.¹¹ We also identified that readily available Ni(ClO₄)₂·6H₂O was comparably effective (entry 2), while NiBr₂ was inferior (entry 3). Use of 5 mol % Ni catalyst resulted in 3 in 78% yield with slightly enhanced E selectivity (entry 4). Lowering the loading of 2 to 1.5 equivalents also afforded 3 in good yield (entry 5). Changes of other parameters such as solvents, reductants, temperatures did not result in better outcomes (entries 6–9). Utilization of E-vinyl bromides only led to E-product, whereas isomerization of the pure Z-vinyl substrate was detect, which gave an E/Z ratio of 16/84 (entries 10–11). The reason for partial isomerization of the Z-vinyl groups under the Ni/Mn conditions is not clear at this time.¹⁷ Finally, the bromo analog of 1 also generated 3 in equally good yield when MgCl₂ was added (entries 12-13).

Table 1. Optimization for the coupling of 1 and 2.^{a,b}

 ^o Center for Supramolecular Chemistry and Catalysis, and Department of Chemistry, Shanghai University, 99 Shang-Da Road, Shanghai 200444, China
 ^b College of Chemical and Environmental Engineering, Shanghai University of Technology, 100 Hai-Quan Road, Shanghai 201418, China.

^{*}Hegui_gong@shu.edu.cn; yao850618jp@yahoo.co.jp; zxhxmu@126.com. †Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

COMMUNICATION





Table 2. Substrate scope for the coupling of α -halo carbonyl compounds with β -styrenyl bromide derivatives.^{*a,b,c*}



^α Standard conditions following method A as in Table 1, entry 1; unless otherwise noted α-chlorocarbonyl substrates were used. ^β Isolated yields. ^c The ratio of *E/Z* > 99:1 for the vinyl bromide. ^α The ratio of *E/Z* = 84:16 for (2-bromovinyl)benzene. ^α

E/Z ratios were obtained by GC. ^f The bromo carbonyl substrate was used with addition of 1 equiv of MgCl₂. View Article Online DOI: 10.1039/C6OB02269C





^α Method B: α-halocarbonyl compounds (0.15 mmol), **2** (0.3 mmol), Ni(COD)₂ (0.015 mmol), pyridine (0.15 mmol), 2,2'-bipyridine (0.045 mmol), Mn (0.3 mmol), DMA (1 mL), 25 °C. ^a Isolated yields. ^c The *E/Z* ratios were determined by GC. ^a α Chloro ester was used. ^e α-Bromo carbonyl compounds were used with addition of 1 equiv of MgCl₂. ^f 1-Bromo-1-propene with *E/Z* ratio of 40/60. ^g The *E* vinyl bromide was used (E/Z > 99:1). ^h1-Bromo-1-nonene with *E/Z* ratio of 35/65.

Scheme 2. Method B for the coupling of 1b with 1-bromo-1propene.



A survey of a wide range of α -halo carbonyl compounds with a set of β -styrenyl bromide derivatives was carried out using the standard method A (Table 1, entry 1). Variations of the substituents on the phenyl rings of the vinyl bromides generated the products **4–10** in good to excellent yields, indicating that the electronic properties of the conjugated arenes had a minor impact on the coupling efficiency. However, use of the sterically more demanding (*E*)-(1-bromoprop-1en-2-yl)benzene gave **11** in diminished yield. Other alkyl 2chloropropanoate derivatives also proved to be effective, as evident in the products **12–14**. Vinyl bromides conjugated with naphthyl, furyl, and styrenyl were all competent, providing **14–16** in good yields. Moreover, the sterically more congested 2-bromohexanoate

Journal Name

Published on 15 November 2016. Downloaded by Athabasca University on 16/11/2016 01:30:33

Journal Name

resulted in the vinyl products 17--18 in satisfactory outcomes. The present protocol was also applicable to $\alpha\text{-bromoamides}$, wherein use of MgCl₂ as the additive was necessary, as manifested by the products 19--21.

Extension of the optimized method A to alkyl-substituted vinyl bromides was not satisfying. The coupling of ${\bf 1b}$ with 1-bromo-1propene only resulted in the product 36 in 10% yield. The yield was boosted to 86% upon addition of 2,2'-bipyridine, wherein the E/Z ratio of the starting vinyl group changed from 40/60 to 78/22 in the product (Scheme 2). The coupling conditions displayed remarkable compatibility with α -vinyl bromides, which has been sparsely addressed in the concurrent reductive vinylation work.7b,11 Excellent yields were obtained for 23-24. It should be noted that preparation of α, α -dialkyl-substituted olefins remains a challenge using Heck methods.¹⁸ For phenyl 2-bromobutanoate, MgCl₂ was added, which resulted in 25-26 in good yields. Likewise, the sterically more bulky 2-bromohexanoate was also competent for the coupling with (E)-2bromo-1-butene, 1-bromo-2-methyl-1-propene and (E)-(4-bromo-3buten-1-yl)benzene, which delivered 27-29 in good to excellent yields. The compatibility of 2-bromoamides was examined for the coupling with both α - and β -vinyl bromides. The vinylated amide products 30-34 were obtained in good to excellent yields. Partial conversions of the (Z)-vinyl groups of the halides to E-products were also observed; 1-bromo-1-nonene with an E/Z ratio of 35/65 resulted in that of 75/25 for 30 and 85/15 for 34, respectively.

In light of the previous mechanistic studies on the vinylation and arylation of alkyl halides, 7,19 we propose that this coupling event proceeds through a radical-chain process wherein oxidative addition of vinyl halides to Ni⁰ generates vinyl–Ni^{II} intermediates (Scheme 3). The combination of a cage-escaped alkyl radical with the vinyl–Ni^{II} species generates a Ni^{III} complex that results in the product and L_n–Ni^I–X upon reductive elimination. Halide abstraction or one-electron reduction of alkyl halides by the Ni^I intermediate affords radicals and a Ni^{III} species, which is reduced to Ni⁰ by Mn, allowing the catalytic process to continue (Scheme 3).

Scheme 3. Proposed catalytic cycle for the vinylation process.



Conclusions

In summary, we have demonstrated that vinylation of α -halo carbonyl compounds with vinyl halides can be readily achieved under mild, Ni-catalyzed reductive coupling conditions. For aryl-conjugated vinyl halides, pyridine serves as the only labile ligand, whereas for alkyl-decorated vinyl halides, the use of pyridine and bipyridine necessitates the coupling event. In the latter case, α -vinyl functional groups can be effectively incorporated. Both 2-haloesters and - amides are suited for the coupling process, which afford the vinylated products in good to high yields with excellent functional

COMMUNICATION

group tolerance. Whereas the *E*-vinyl halides generates exclusively *E*-products, the *Z*-vinyl groups in the vinyl halides were moderately converted to the *E*-products.

Acknowledges

Financial support was provided by the Chinese NSF (Nos. 21172140, 21302127, 21372151 and 21572127), Shanghai Municipal Education Commission for the Programs for Professor of Special Appointment (Dongfang Scholarship) and Peak Discipline Construction (N.13-A302-15-L02) and Shanghai Science and Technology Commission (14DZ2261100). Dr. Hongmei Deng (Shanghai Univ.) is thanked for use of the NMR facility.

Notes and references

- Synthetic buiding blocks: (a) T. Ankner, C. C. Cosner and P. Helquist, Chem.—Eur. J., 2013, **19**, 1858; (b) J. A. Gurak, Jr, K. S. Yang, Z. Liu and K. L. Engle, *J. Am. Chem. Soc.*, 2016, **138**, 5805.
- Bioactive: (a) H. Irschik, P. Washausen, F. Sasse, J. Fohrer, V. Huch, R. Müller and E. V. Prusov, *Angew. Chem., Int. Ed.*, 2013, 52, 5402;
 (b) N. Tsuji, M. Kobayashi, K. Nagashima, Y. Wakisaka and K. J. Koizumi, *Antibiot.*, 1976, 29, 1; (c) Y. Liu, S. C. Virgil, R. H. Grubbs and B. M. Stoltz, *Angew. Chem., Int. Ed.*, 2015, 54, 11800–11803;
 (d) R. V. Edwankar, C. R. Edwankar and J. M. Cook, *J. Org. Chem.*, 2014, 79, 10030.
- 3 (a) M. Grigalunas, T. Ankner, P.–O. Norrby, O. Wiest and P. Helquist, Org. Lett., 2014, 16, 3970; (b) Pd: J. Huang, E. Bunel and M. M. Faul, Org. Lett., 2007, 9, 4343-4346; (c) A. Chieffi, K. Kamikawa, A. Ahman, J. M. Fox and S. L. Buchwald, Org. Lett., 2001, 3, 1897; (d) X. Liu and J. F. Hartwig, Org. Lett., 2003, 5, 1915.
- 4 Ni-catalyzed alkenylation of enolates, see: M. Grigalunas, T. Ankner, P.–O. Norrby, O. Wiest and P, Helquist, *J. Am. Chem. Soc.*, 2015, **137**, 7019.
- 5 For oxidative coupling of enolates with vinylmetallic reagents, see: (a) E. Eduardas Skucas and D. W. C. MacMillan, J. Am. Chem. Soc., 2012, **134**, 9090–9093; (b) J. M. Stevens and D. W. C. MacMillan, J. Am. Chem. Soc., 2013, **135**, 11756; (c) H. Kim and MacMillan, J. Am. Chem. Soc., 2008, **130**, 398.
- 6 (a) S. Lou and G. C. Fu, J. Am. Chem. Soc., 2010, 132, 5010; (b) X. Dai, N. A. Strotman and G. C. Fu, J. Am. Chem. Soc., 2008, 130, 3302.
- 7 (a) D. A. Everson, B. A. Jones and D. J. Weix, *J. Am. Chem. Soc.*, 2012, **134**, 6146; (b) K. A. Johnson, S. Soumik Biswas and D. J. Weix, *Chem. —Eur. J.*, 2016, **22**, 7399.
- 8 For Pd-catalyzed in situ Negishi coupling, see: A. Krasovskiy, C. Duplais and B. H. Lipshutz, *Org. Lett.*, 2010, **12**, 4742.
- 9 For the photoredox/Ni-catalyzed methods, see: (a) N. R. Patel, C.
 B. Kelly, M. Jouffroy and G. A. Molander, *Org. Lett.*, 2016, 18, 764;
 (b) A. Noble, S. J. McCarver and D. W. MacMillan, *J. Am. Chem. Soc.*, 2015, 137, 624.
- 10 For reviews on reductive coupling of two electrophiles, see: (*a*) C.
 E. I. Knappke, S. Grupe, D. Gärtner, M. Corpet, C. Gosmini and A.
 J. Wangelin, *Chem. –Eur. J.*, 2014, **20**, 6828; (*b*) D. A. Everson and
 D. J. Weix, *J. Org. Chem.*, 2014, **79**, 4793; (*c*) T. Moragas, A. Correa and R. Martin, *Chem. –Eur. J.*, 2014, **20**, 8242; (*d*) D. J. Weix, *Acc. Res. Chem.*, 2015, **48**, 1767; (*e*) J. Gu, X. Wang, W. C. Xue and G.
 H. Gong, *Org. Chem. Front*, 2015, **2**, 1411.
- 11 Ni-catalyzed electrochemical: C. Cannes, S. Condon, M. Durandetti, J. Périchon and J.-Y. Nédélec, J. Org. Chem., 2000, 65, 4575-4583.

Published on 15 November 2016. Downloaded by Athabasca University on 16/11/2016 01:30:33

- M. Durandetti, C. Gosmini and J. Perichon, *Tetrahedron*, 2007, 63, 1146.
- 13 For Ni-catalyzed reductive arylation of unactivated alkyl halides, see: (a) S. Wang, Q. Qian and H. Gong, Org. Lett., 2012, 14, 3352; (b) D. A. Everson, R. Shrestha and D. J. Weix, J. Am. Chem. Soc., 2010, 132, 920; (c) C.-S. Yan, Y. Peng, X.-B. Xu and Y.-W. Wang, Chem.-Eur. J., 2012, 18, 6039; (d) Everson, D. A.; Jones, B. A.; Weix, D. J. J. Am. Chem. Soc. 2012, 134, 6146; (e) G.A. Molander, K. M. Traister and B. T. O'Neill, J. Org. Chem., 2015, 80, 2907. (f) Y. Peng*, J. Xiao, X.-B. Xu, S.-M. Duan, L. Ren, Y.-L. Shao, and Y.-W. Wang, Org. Lett. 2016, 18, 5170; (g) Y. Peng, X.-B. Xu, J. Xiao, Y.-W. Wang, Chem. Commun. 2014, 50, 472.
- 14 (a) A.H. Cherney, N. T. Kadunce and S. E. Reisman, J. Am. Chem. Soc., 2013, 135, 7442; (b) A. H. Cherney, and S. E. Reisman, J. Am. Chem. Soc., 2014, 136, 14365; (c) N.T. Kadunce and S.E. Reisman, J. Am. Chem. Soc., 2015, 137, 10480.
- 15 Y. Peng, L. Luo, C.-S. Yan, J.-J. Zhang and Y.-W. Wang, J. Org. Chem., 2013, 78, 10960.
- 16 For pyridine-promoted arylation of *tertiary* alkyl halides, see: X. Wang, S. Wang, W. Xue and H. Gong, J. Am. Chem. Soc., 2015, **137**, 11562.
- 17 The reason for isomerization of vinyl halides under Ni- or Cocatalyzed conditions have been discussed, but no conclusive remarks have been reached, see Ref. 7b and (a) A. Moncomble, Pascal Le Floch, A. Lledos and C. Gosmini, J. Org. Chem., 2012, 77, 5056. However, it is likely that the formation of a zwitterionic C(carbene)-Ni intermediate accounts for this transformation, see: (b) J. M. Huggins and R. G. Bergman J. Am. Chem. Soc. 1981, 103, 3002; (c) C. Clarke, C. A. Incerti-Pradillos and H. W. Lam, J. Am. Chem. Soc. 2016, 138, 8068.
- 18 For selected examples, see: (a) T. Nishikata, K. Nakamura, K. Itonaga and S. Ishikawa, Org. Lett., 2014, 16, 5816–5819; (b) K. S. Bloome, R. L. McMahen and E. J. Alexanian, J. Am. Chem. Soc., 2011, 133, 20146; (c) C. Liu, S. Tang, D. Liu, J. Yuan, L. Zheng, L. Meng and A. Lei, Angew. Chem., Int. Ed., 2012, 124, 3698; (d) R. Matsubara, A. C. Gutierrez and T. F. Jamison, J. Am. Chem. Soc., 2011, 133, 19020.
- 19 S, Biswas and D. J. Weix, J. Am. Chem. Soc., 2013, 135, 16192.

Page 4 of 4

View Article Online DOI: 10.1039/C6OB02269C