

Conference paper

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HOME-Chemistry: hydrazone as organo-metallic equivalent

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Abstract: The modern synthetic chemistry heavily relies on the use of stoichiometric organometallic reagents to react with various electrophiles. The dependence on stoichiometric quantities of metals and often organic halides as precursors, in turn both produces copious amounts of metal halide wastes as well as leads to concerns on future metal sustainability. Inspired by the classical Wolff-Kishner reduction, our lab has recently developed a general strategy of **HOME-Chemistry**, directly using naturally abundant alcohols/aldehydes and ketones as feedstocks with the releasing of innocuous water and nitrogen gas. These reactions include 1,2-carbonyl/imine addition, conjugate addition, carboxylation, olefination, cross-coupling arylation/allylation, alkylation, hydroalkylation and C-heteroatom formations. This article provides a brief summary on this chemistry.

Keywords: Coupling reactions; HOME-Chemistry; ICGC-9; metal sustainability; organometallic reagents; umpolung hydrazone.

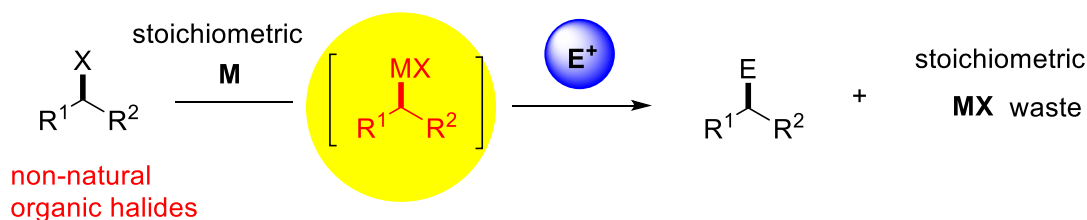
Introduction

The classical and modern synthetic chemistry profoundly relies on the use of various organometallic (and metalloids) reagents (Fig. 1a) [1] to react with diverse electrophiles, producing >30 named reactions in organic chemistry, and are subjects of 1912, 1979 and 2010 Nobel Prizes [2]. Although such organometallic reactions are highly effective in fine chemicals, pharmaceutical, agrochemicals and organic materials, such reliance on stoichiometric organometallic reagents raised serious concerns in many aspects in the eyes of Green Chemistry [3]: 1) organometallic reagents are most widely prepared from non-natural organic halides; 2) most organometallic reagents can not tolerate natural environment of air, water and various functional groups, and thus are generally operated under inert atmosphere, in anhydrous organic solvents with the functional groups being protected; 3) the mining, processing and transporting of metals are limited by various factors; 4) these reactions inevitably generate stoichiometric quantities of metal salt wastes. For many years, we have been compounding the possibility of innovative scientific means to turn naturally abundant C–OH and C=O bonds into equivalents of organometallic reagents but without resulting stoichiometric metals. In 2010, our lab came up with a strategy via hydrazone intermediate with the help of transition-metal catalysis [4]. As the scope of this research has vastly broadened, it is necessary to give a simple representation of such chemistry. Consequently, we termed it **Hydrazone as Organo-Metallic Equivalent (HOME)** (Fig. 1b).

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(A) Classical Organometallic Reactions



(B) HOME: Hydrazone as Organo-Metallic Equivalent

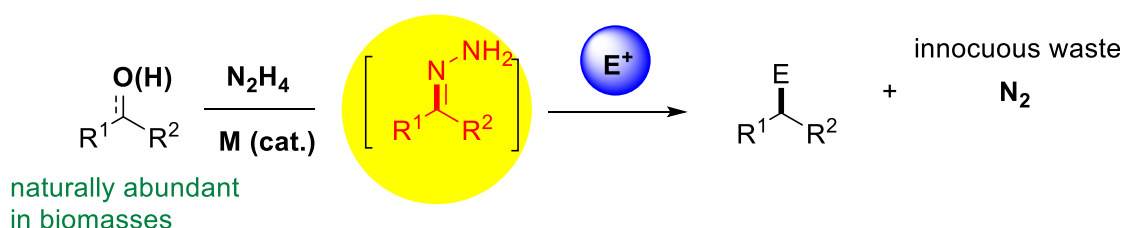


Fig. 1: General methods for bond formations with electrophiles.

Background

Our interest in developing novel methods towards greener C–C bond formations started with the concurrent emerging of Green Chemistry. Our first objective was to overcome the limitation of water and functional tolerance limitations of organometallic reactions by developing such reactions in water to circumvent functional group protection-deprotections [5]. Our second objective was to simplify halogenation-dehalogenation via C–H functionalization such as the aldehyde-alkyne-amine (A^3 -coupling) reactions also mostly in water [6]. Our third objective was to simplify the requirement of functional groups by directly forming C–C bonds from two different C–H bonds via the formal removal of “H₂”, termed Cross-Dehydrogenative Couplings (CDC) [7]. All three aspects have spurred tremendous research activities and achievements by numerous researchers. In spite of these great successes, organic halides are not naturally abundant; while to control the selective reaction of many different C–H bonds in organic molecules is challenging and often requires directing groups.

Alternatively, most naturally occurring and renewable biomass feedstocks, such as carbohydrates and lignin cellulose, have abundant C–OH and C=O bonds already in place. Hence, for over a decade, we have been contemplating an innovative solution to this challenging problem.

Conceptual design

In 2010, we came up with an idea, which was inspired by the classical Wolff-Kishner reduction (Fig. 2a) [8] and the “borrowing hydrogen” strategy for the conversion of alcohols to amines (Fig. 2b) [9]. We reasoned that if we replace the amine by hydrazine, then a hydrazone intermediate will be formed. Unlike the borrowing hydrogen strategy in which the hydrogens are added back, the hydrazone intermediate coordinated with the transition-metal catalyst can selectively react with various electrophiles with controlled reactivity by modulating the transition-metal and the coordinating ligand (Fig. 2c). In addition, unlike classical “hard” organometallic reagents, such coordinated complexes are “soft” and can tolerate various “hard” protonated functional groups and water.

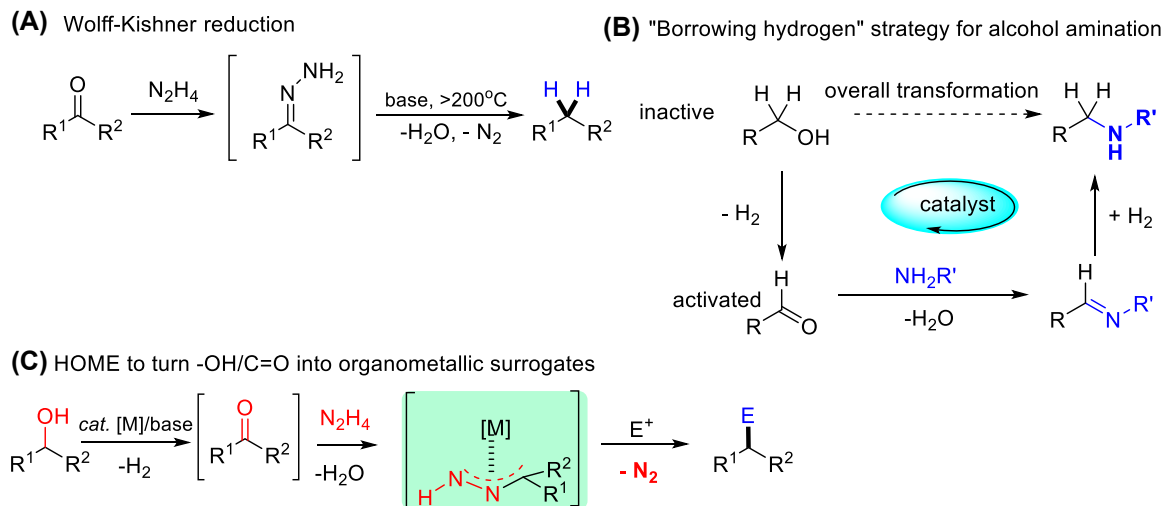


Fig. 2: HOME-Chemistry inspired by the Wolff-Kishner reduction and "borrowing hydrogen" strategy.

Furthermore, the reactivity as well as the chemo, regio, stereo and enantioselectivities of such complexes can be readily tuned by modifying the metal center and ligand. The coordination of hydrazone with transition-metal can also significantly increase the acidity of NH_2 group in hydrazone, allowing deprotonation under very mild conditions. It is important to note that the current nitrogen fixation method via the Haber-Bosch process is highly energy intensive, due to the generation of hydrogen gas and the requirement of high temperature and pressure. However, recent and possible future developments in the direct conversion of nitrogen to hydrazine under ambient conditions with "green energy" will make this process also energetically favorable [10].

Protonation

We commenced our research by looking at such organometallic reagent surrogates with the simplest electrophile, H^+ . While most research efforts involve how to add functional groups, methods to deoxygenate an alcohol are very rare and mostly done by the Barton-McCombie reaction [11]. We found that using Ir [12] and Ru [13] catalysts, alcohols can be directly removed with hydrazine, via dehydrogenating to aldehyde by the transition-metal catalyst and forming coordinated-hydrazone with hydrazine *in situ* (Fig. 3a). Denitrogenation of the hydrazone intermediate under mild conditions gives the alcohol deoxygenated product. Primary alcohols can be selectively deoxygenated and a wide range of functional groups such as carboxylic acid, secondary alcohols and amines can be tolerated. The reaction can also be carried out **in water**. In addition, the deoxygenation can also be carried out without metal catalyst by irradiation with UV light at room temperature [14]. Instead of using alcohols, aldehydes and ketones can be directly deoxygenated to CH_2 group in water or alcohol (Fig. 3b) [15], equivalent to the Wolff-Kishner reduction but under much milder conditions.

1,2-Nucleophilic additions

Having succeeded the protonation, we then moved to the more synthetically useful 1,2-nucleophilic additions, leading to Grignard-type reaction products but without using Grignard reagents. We found that Ru [16] and Fe [17] based catalysts can effectively catalyze such additions to carbonyl compounds, imines [18] and CO_2 [19] (Fig. 4a). With ruthenium as catalyst, the reaction can be carried out in water [20]. With the Fe-based catalyst, such nucleophilic additions can occur even at room temperature. Combining a chiral ligand with the ruthenium catalyst, enantioselective nucleophilic addition is also possible. Furthermore, using a ruthenium catalyst,

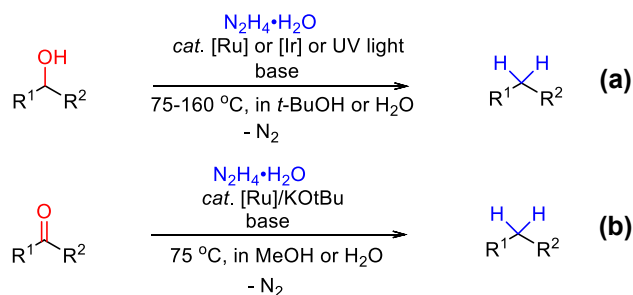


Fig. 3: Direct deoxygenation of alcohols and aldehydes/ketones via HOME.

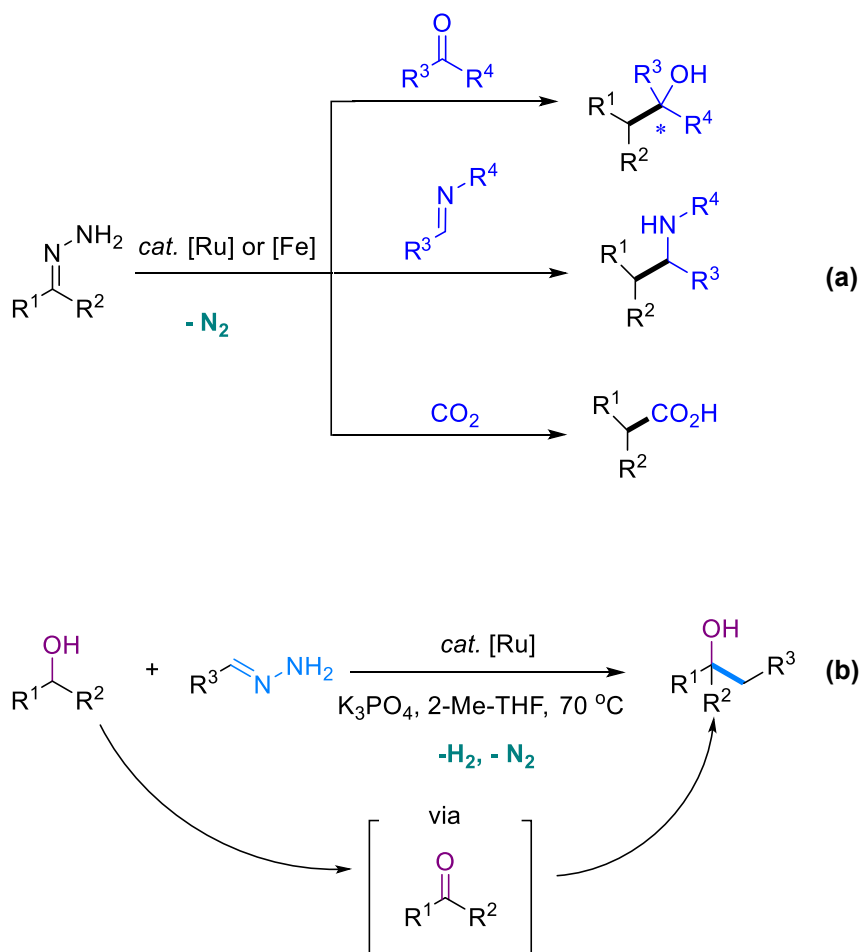


Fig. 4: Catalytic nucleophilic addition of hydrazone via HOME.

hydrazones can add to simple alcohols and olefinic alcohols directly [21], in which one hydrogen is replaced by an alkyl group and the more abundant alcohol groups serve as equivalents of less available carbonyls, not being possible for the classical Grignard-type chemistry (Fig. 4b).

Conjugate additions

Another important classical organometallic reaction is the conjugate addition mediated by copper. We found that Ru [22], Fe, and Cu [23] catalysts can all catalyze the conjugate addition of hydrazones to various electron-deficient

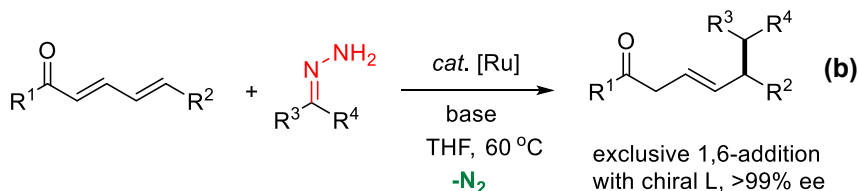
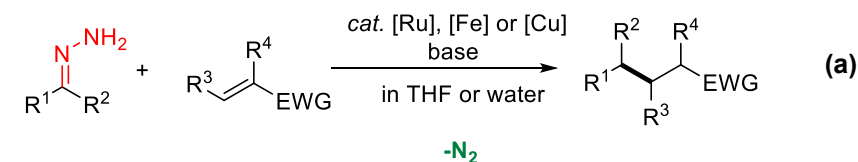


Fig. 5: Catalytic conjugate addition of hydrazone via HOME.

double bonds (Fig. 5a). For electron-deficient dienes with an extended conjugation, the Ru-catalyst gives exclusively terminal regioselectivity, and a very high enantioselectivity with a chiral phosphine ligand (Fig. 5b) [24].

Olefination

By tuning the reaction conditions, cross-olefination products can be obtained efficiently by generating a hydrazone intermediate between the first carbonyl and hydrazine, which then reacts with the second carbonyl catalyzed by ruthenium (Fig. 6a) [25]. Milstein shows that it is also possible to couple the hydrazone with another alcohol to generate the olefination product with a manganese catalyst (Fig. 6b) [26]. By using a nickel catalyst, ketones can be directly converted into olefins, providing a simpler version of the classical Shapiro reaction (Fig. 6c) [27].

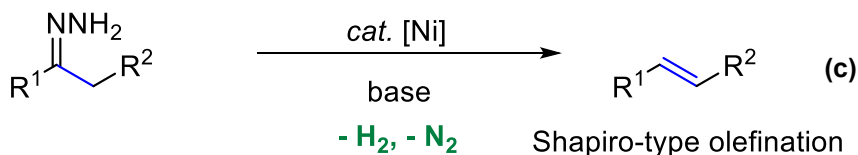
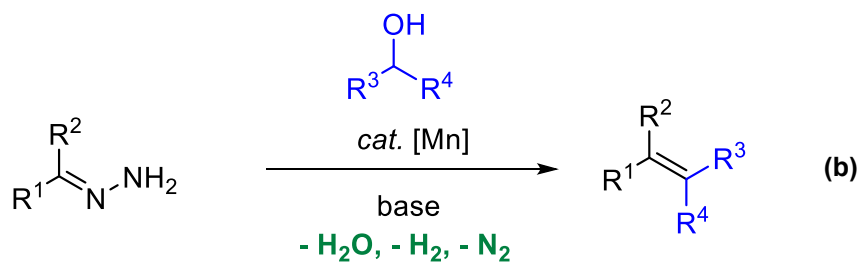
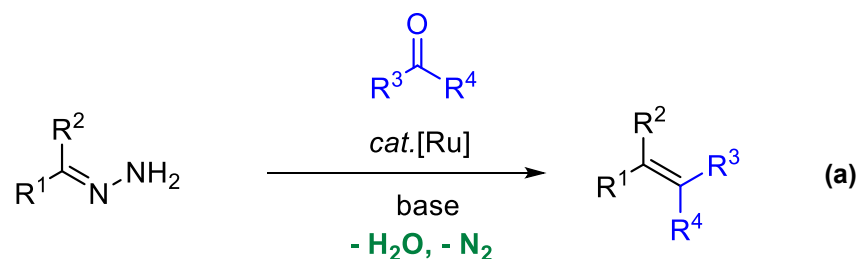


Fig. 6: Catalytic olefination of hydrazone via HOME.

Cross-couplings

One of the most important modern achievements in synthetic chemistry is the development of transition-metal catalyzed cross-coupling reactions with organometallic reagents. We have demonstrated that Ni [28], Co [29] and Ru [30] can catalyze various cross-couplings between hydrazone and aryl/alkyl electrophiles under mild conditions or under visible light irradiation in absence of transition-metal catalyst [31] (Fig. 7a), an alternative to

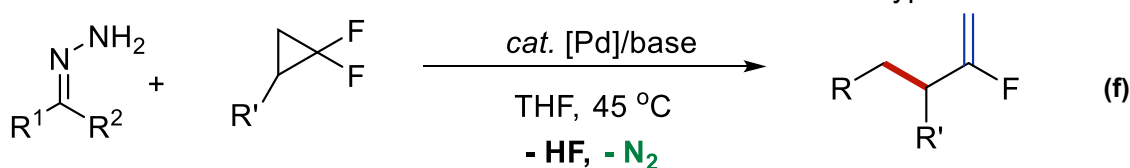
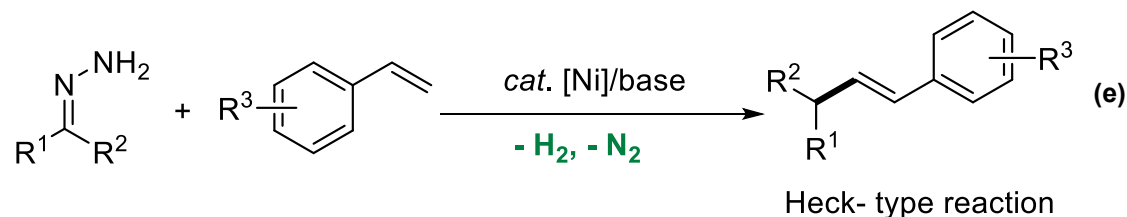
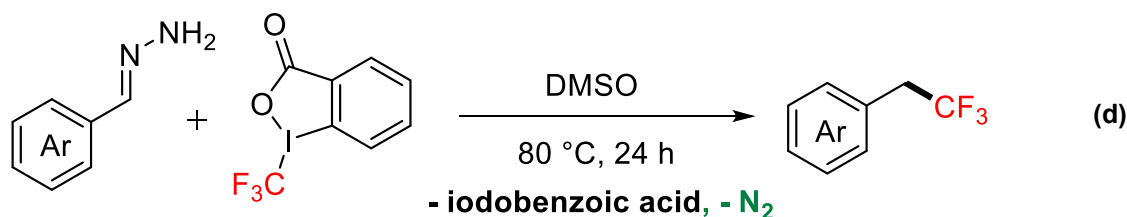
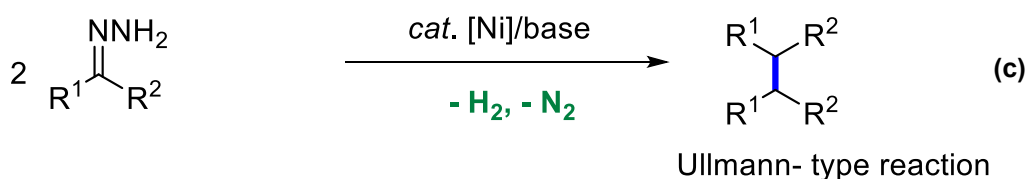
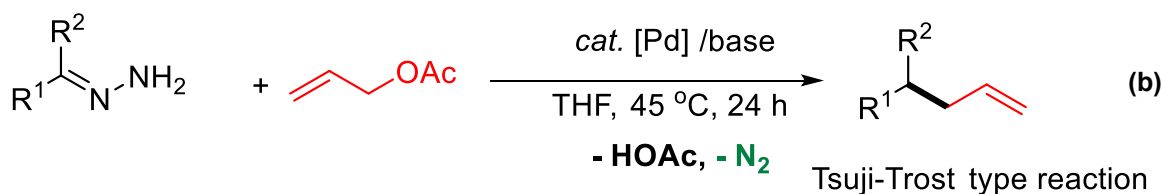
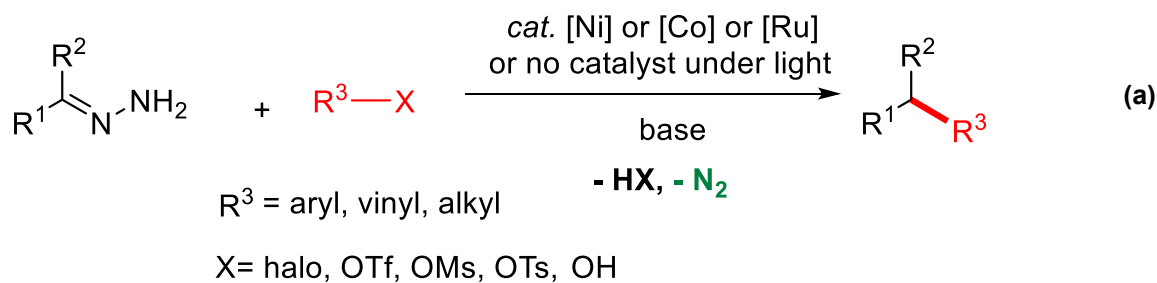


Fig. 7: Diverse cross-coupling reactions via HOME.

Suzuki/Negishi couplings. The Pd-catalyzed Tsuji-Trost type allylation with hydrazone can be carried out with palladium catalyst (Fig. 7b) [32]. With a nickel catalyst, two carbonyls can be homolytically joined as simple C–C coupled products via hydrazones, an alternative to the Ullmann-type coupling reaction (Fig. 7c) [33]. Trifluoromethylation can be achieved directly between hydrazones and a high-valent trifluoromethylating reagent (Fig. 7d) [34]. With a nickel catalyst, a dehydrogenative Heck-type reaction occurs between hydrazones and styrene derivatives (Fig. 7e) [35]. Also, with a palladium catalyst, hydrazones can couple with gem-difluorocyclopropane via a defluoro-ring opening process (Fig. 7f) [36].

Hydroalkylations

In the presence of a ruthenium catalyst, hydrazones can efficiently add to vinyl pyridines (Fig. 8a) [37], conjugated enynes and dienes (Fig. 8b) [38]. With a nickel catalyst, hydrazones can also add to dienes to give internal addition products (Fig. 8c) [39], complimenting to the terminal selectivity catalyzed by ruthenium. Using a palladium

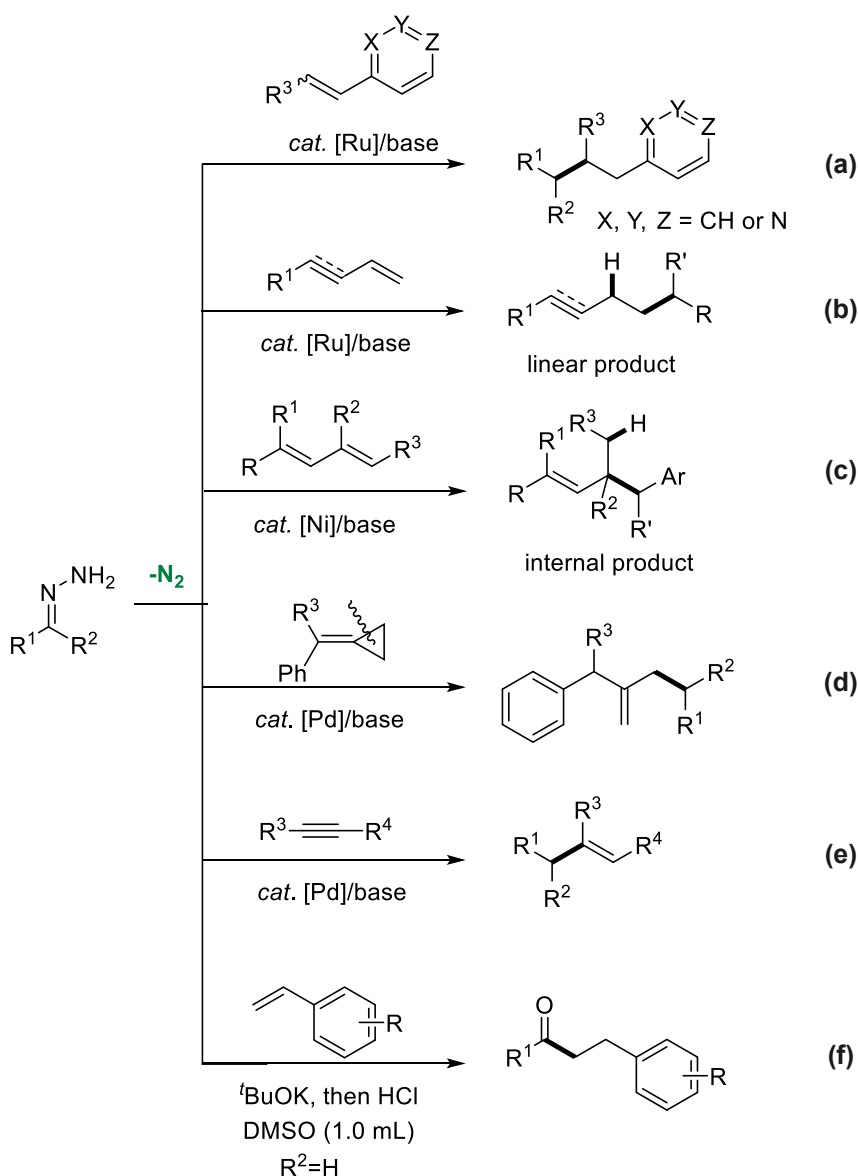


Fig. 8: Hydroalkylation of alkene, alkyne, diene, enyne and vinylcyclopropane via HOME.

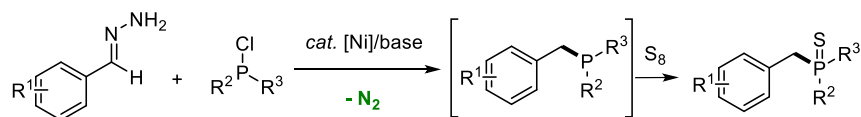


Fig. 9: Ni-catalyzed Csp³-P(III) cross-coupling of hydrazones and phosphine chlorides via HOME.

catalyst, hydrazone can react with vinyl propene (Fig. 8d) [40] and alkynes, providing hydroalkylation products with excellent regio and syn-addition selectivity for the latter (Fig. 8e) [41]. In absence of transition-metal catalyst, hydrazones can add to styrene derivatives under basic conditions to give carbonyl compounds upon acidic workup (Fig. 8f) [42].

Forming C-heteroatom bonds

Lastly, organometallic reagents have been widely used to react with non-carbon electrophiles. Similar to organometallic reagents, hydrazones can react with dialkylphosphinyl chloride, generating highly valuable trivalent phosphine compounds in the presence of a nickel catalyst (Fig. 9) [43]. The air-sensitive products were isolated as sulfides, which can be turned back to trivalent phosphines readily.

Summary and future perspectives

In conclusion, while classical organometallic reagents are central to the state-of-art chemical transformations, the requirement of stoichiometric metals, the often-needed organic halide feedstocks, and their intolerance of water and common functional groups raise concerns of metal sustainability, synthetic inefficiency and waste-generations. Our recent studies show that HOME-Chemistry has the potential to provide an alternative to a wide range of classical organometallic reactions, which are based on naturally abundant –OH and C=O groups, have good tolerance of various functional groups and water, and release nitrogen gas as an innocuous by-product. As an example, free sugars can be directly converted to C–C bond derivatives via this chemistry (Fig. 10) [44]. The HOME-Chemistry is likely to open a new avenue for future organometallic reactions.

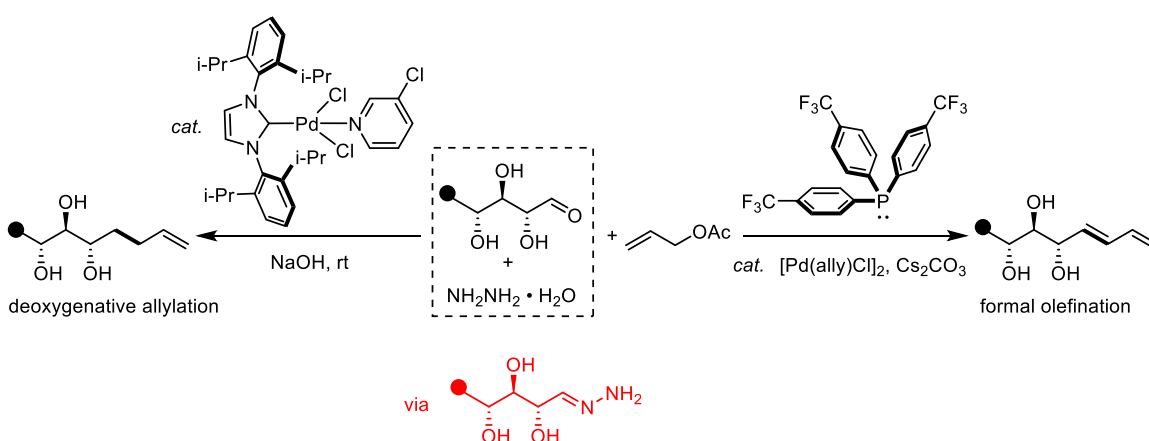


Fig. 10: Palladium-catalyzed C–C bond formation of native carbohydrates via HOME.

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References

- [1] J. H. Bateso, M. B. Mitchell (Eds.). *Organometallic Reagents in Organic Synthesis*, Academic Press, London (1994).
- [2] P.-Q. Huang. *Organic Name Reactions, Reagents, and Rules*, Chemical Industry Press, Beijing, 2nd ed. (2019).
- [3] P. T. Anastas, J. C. Warner. *Green Chemistry Theory and Practice*, Oxford University Press, New York (1998).
- [4] C.-J. Li, J. Huang, X. Dai, H. Wang, N. Chen, W. Wei, H. Zeng, J. Tang, C. Li, D. Zhu, L. Lv. *Synlett* **30**, 1508 (2019); C.-J. Li. *The Innovations* **3**, 100262 (2022); X.-J. Dai, C.-C. Li, C.-J. Li. *Chem. Soc. Rev.* **50**, 10733 (2021), <https://doi.org/10.1055/s-0037-1611853>.
- [5] C.-J. Li. *Tetrahedron* **52**, 5643 (1996), [https://doi.org/10.1016/0040-4020\(95\)01056-4](https://doi.org/10.1016/0040-4020(95)01056-4).
- [6] C. Wei, C.-J. Li. *J. Am. Chem. Soc.* **124**, 5638 (2002), <https://doi.org/10.1021/ja026007t>.
- [7] C.-J. Li. *Acc. Chem. Res.* **42**, 335 (2009), <https://doi.org/10.1021/ar800164n>.
- [8] D. E. Lewis. *The Wolff–Kishner Reduction and Related Reactions: Discovery and Development*, D. E. Lewis (Ed.), Elsevier, Amsterdam (2019).
- [9] A. J. A. Watson, J. M. J. Williams. *Science* **329**, 635 (2010), <https://doi.org/10.1126/science.1191843>.
- [10] P. Saha, S. Amanullah, A. Dey. *J. Am. Chem. Soc.* **142**, 17312 (2020), <https://doi.org/10.1021/jacs.0c08785>.
- [11] D. Barton, S. McCombie. *J. Chem. Soc., Perkin Trans. 1*, 1574 (1975), <https://doi.org/10.1039/p19750001574>.
- [12] J.-L. Huang, X.-J. Dai, C.-J. Li. *Eur. J. Org. Chem.*, 6496 (2013), <https://doi.org/10.1002/ejoc.201301293>.
- [13] X.-J. Dai, C.-J. Li. *J. Am. Chem. Soc.* **138**, 5433 (2016), <https://doi.org/10.1021/jacs.6b02344>.
- [14] D. Cao, Z. Chen, L. Lv, Y. Peng, C.-J. Li. *iScience* **23**, 101419 (2020), <https://doi.org/10.1016/j.isci.2020.101419>.
- [15] R. Gui, C.-J. Li. *Chem. Commun.* **58**, 10572 (2022), <https://doi.org/10.1039/d2cc03326g>.
- [16] H. Wang, X.-J. Dai, C.-J. Li. *Nat. Chem.* **9**, 374 (2017), <https://doi.org/10.1038/nchem.2677>.
- [17] C.-C. Li, X.-J. Dai, H. Wang, D. Zhu, J. Gao, C.-J. Li. *Org. Lett.* **20**, 3801 (2018), <https://doi.org/10.1021/acs.orglett.8b01391>.
- [18] N. Chen, X.-J. Dai, H. Wang, C.-J. Li. *Angew. Chem. Int. Ed.* **56**, 6260 (2017), <https://doi.org/10.1002/anie.201610578>.
- [19] S.-S. Yan, L. Zhu, J.-H. Ye, Z. Zhang, H. Huang, H. Zeng, C.-J. Li, Y. Lan, D.-G. Yu. *Chem. Sci.* **9**, 4873 (2018), <https://doi.org/10.1039/c8sc01299g>.
- [20] Y.-Z. Wang, Q. Liu, L. Cheng, S.-C. Yu, L. Liu, C.-J. Li. *Tetrahedron* **80**, 131889 (2021), <https://doi.org/10.1016/j.tet.2020.131889>.
- [21] C.-C. Li, H. Wang, M. M. Sim, Z. Qiu, Z.-P. Chen, R. Z. Khaliullin, C. J. Li. *Nat. Commun.* **11**, 6022 (2020); C.-C. Li, J. Kan, Z. Qiu, J. Li, L. Lv, C.-J. Li. *Angew. Chem. Int. Ed.* **59**, 4544 (2020), <https://doi.org/10.1038/s41467-020-19857-9>.
- [22] X.-J. Dai, H. Wang, C.-J. Li. *Angew. Chem. Int. Ed.* **56**, 6302 (2017), <https://doi.org/10.1002/anie.201700059>.
- [23] S. Luo, M. Peng, P. Querard, C.-C. Li, C.-J. Li. *J. Org. Chem.* **86**, 13111 (2021), <https://doi.org/10.1021/acs.joc.1c01380>.
- [24] H. Kang, C.-J. Li. *Chem. Sci.* **13**, 118 (2022), <https://doi.org/10.1039/d1sc03732c>.
- [25] W. Wei, X.-J. Dai, H. Wang, C. Li, X. Yang, C.-J. Li. *Chem. Sci.* **8**, 8193 (2017), <https://doi.org/10.1039/c7sc04207h>.
- [26] U. K. Das, S. Chakraborty, Y. Diskin-Posner, D. Milstein. *Angew. Chem. Int. Ed.* **57**, 13444 (2018), <https://doi.org/10.1002/anie.201807881>.
- [27] S. Xia, D. Cao, H. Zeng, L.-N. He, C.-J. Li. *J. Am. Chem. Soc. Au* **2**, 1929 (2022), <https://doi.org/10.1021/jacsau.2c00320>.
- [28] J. Tang, L. Lv, X.-J. Dai, C.-C. Li, L. Li, C.-J. Li. *Chem. Commun.* **54**, 1750 (2018), L. Lv, D. Zhu, J. Tang, Z. Qiu, C.-C. Li, J. Gao, C.-J. Li. *ACS Catal.* **8**, 4622 (2018); D. Zhu, L. Lv, Z. Qiu, C.-J. Li. *J. Org. Chem.* **84**, 6312 (2019); see also: C. Zhu, J. Zhang. *Chem. Commun.* **55**, 2793 (2019), <https://doi.org/10.1039/c7cc09290c>.
- [29] R. Cheng, G. de Ruiter, C.-J. Li. *Chem. Commun.* **58**, 11563 (2022), <https://doi.org/10.1039/d2cc04302e>.
- [30] D. Cao, P. Pan, H. Zeng, C.-J. Li. *Chem. Commun.* **55**, 9323 (2019), <https://doi.org/10.1039/c9cc04299g>.
- [31] P. Pan, S. Liu, Y. Lan, H. Zeng. *Chem. Sci.* **13**, 7165 (2022), <https://doi.org/10.1039/d2sc01909d>.
- [32] D. Zhu, C.-C. Li, L. Lv, S. Ung, J. Gao, C.-J. Li. *Angew. Chem. Int. Ed.* **57**, 16520 (2018), <https://doi.org/10.1002/anie.201809112>.
- [33] D. Cao, H. Zeng, Y. Peng, C.-J. Li. *Nat. Commun.* **12**, 3729 (2021), <https://doi.org/10.1038/s41467-021-23971-7>.
- [34] H. Zeng, Z. Luo, X. Han, C.-J. Li. *Org. Lett.* **21**, 5948 (2019), <https://doi.org/10.1021/acs.orglett.9b02072>.
- [35] L. Lv, D. Zhu, C.-J. Li. *Nat. Commun.* **10**, 715 (2019), <https://doi.org/10.1038/s41467-019-08631-1>.
- [36] L. Lv, C.-J. Li. *Angew. Chem. Int. Ed.* **60**, 13098 (2021), <https://doi.org/10.1002/anie.202102240>.
- [37] L. Lv, C.-J. Li. *Chem. Sci.* **12**, 2870 (2021), <https://doi.org/10.1039/d0sc06586b>.
- [38] L. Lv, L. Yu, Z. Qiu, C.-J. Li. *Angew. Chem. Int. Ed.* **59**, 6466 (2020), <https://doi.org/10.1002/anie.201915875>.
- [39] L. Lv, D. Zhu, Z. Qiu, J. Li, C.-J. Li. *ACS Catal.* **9**, 9199 (2019); see also: L. Cheng, M.-M. Li, B. Wang, L.-J. Xiao, J.-H. Xie, Q.-L. Zhou. *Chem. Sci.* **10**, 10417 (2019), <https://doi.org/10.1021/acscatal.9b02483>.
- [40] J. Yao, Z. Chen, L. Yu, L. Lv, D. Cao, C.-J. Li. *Chem. Sci.* **11**, 10759 (2020), <https://doi.org/10.1039/d0sc01221a>.
- [41] L. Yu, L. Lv, Z. Qiu, Z. Chen, Z. Tan, Y.-F. Liang, C.-J. Li. *Angew. Chem. Int. Ed.* **59**, 14009 (2020), <https://doi.org/10.1002/anie.202005132>.

- [42] P. Pan, Y. Lang, D. Cao, H. Zeng, C.-J. Li. *CCS Chem.* **4**, 3254 (2022), <https://doi.org/10.31635/ccschem.022.202101685>.
- [43] R. Cheng, C.-J. Li. "Csp³–P(III) bond formation via cross-coupling of umpolung carbonyls with phosphine halides catalyzed by nickel." *Submitted for publication*.
- [44] J. Kan, Z. Chen, Z. Qiu, L. Lv, C. Li, C.-J. Li. *Sci. Adv.* **8**, eabm6840 (2022), <https://doi.org/10.1126/sciadv.abm6840>.