A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Umpolung Carbonyl Groups as Alkyl Organometallic Reagent Surrogates for Palladium Catalyzed Allylic Alkylation

Authors: Dianhu Zhu, Leiyang Lv, Chen-Chen Li, Sosthene Ung, Jian Gao, and Chao-Jun Li

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201809112
Angew. Chem. 10.1002/ange.201809112

Link to VoR: http://dx.doi.org/10.1002/anie.201809112
http://dx.doi.org/10.1002/ange.201809112

WILEY-VCH

10.1002/anie.201809112

WILEY-VCH

COMMUNICATION

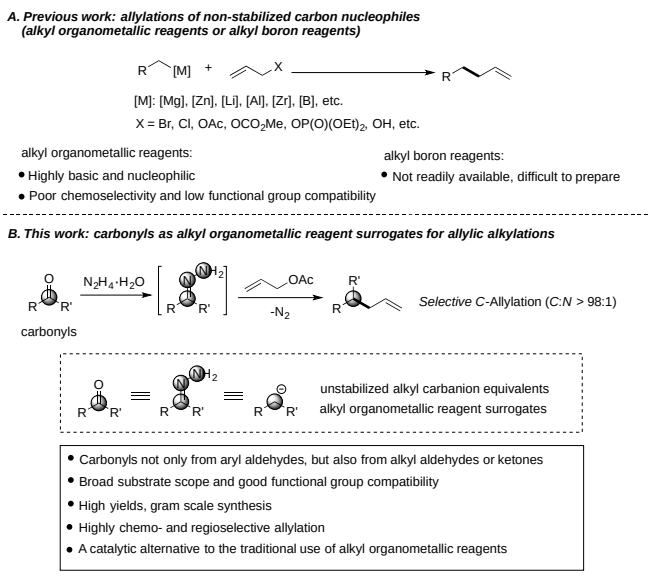
Umpolung of Carbonyl Groups as Alkyl Organometallic Reagent Surrogates for Palladium-Catalyzed Allylic Alkylation

Dianhu Zhu, [+][a] Leiyang Lv, [+][a] Chen-Chen Li, [a] Sosthene Ung, [a] Jian Gao [a] and Chao-Jun Li[a]*

Abstract: *Palladium catalyzed allylic alkylation of non-stabilized carbon nucleophiles is difficult and still remains a major challenge. We report a direct palladium-catalyzed highly chemo- and regioselective C-allylation of hydrazones generated from carbonyls as a source of umpolung unstabilized alkyl carbanions and surrogates of alkyl organometallic reagents. Contrary to classical allylation techniques, this umpolung reaction utilizes hydrazones prepared not only from aryl aldehydes but also from alkyl aldehydes and ketones as renewable feedstocks. This strategy complements the palladium-catalyzed coupling of unstabilized nucleophiles with allylic electrophiles by providing an efficient and selective catalytic alternative to the traditional use of highly reactive alkyl organometallic reagents.*

The Tsuji-Trost reaction has been one of the most important achievements in modern synthetic chemistry by serving as a versatile and powerful synthetic tool for the formation of C-C bonds with a wide range of applications for the synthesis of biologically active molecules.[1-3] There has been a recent increase in the use of newly stabilized nucleophiles[4-5] in order to facilitate and extend the synthetic utility of this reaction. Despite the success of those allylation methods, the use of non-stabilized nucleophiles in palladium-catalyzed allylation is still extremely limited.[6] Traditional allylations of non-stabilized carbon nucleophiles typically involve alkyl organometallic reagents (Scheme 1A). The introduction of the Grignard reagents as cross-coupling partners with allylic substrates represented a major step forward, enabling facile access to a diverse range of alkenes as shown by Swierczewski[7] and Goering.[8] Later, Hoveyda,[9] Feringa,[10] and others.[1] Since then, other alkyl organometallic reagents (such as organozinc,[6a-6b,12] lithium,[13] aluminium[14] or zirconium[15] reagents) and alkyl boron reagents[6d-6e] have also been used for allylations. Although these alkyl organometallic reagents have numerous industrial applications, there are still substantial drawbacks associated with them. The preparation of these air/moisture sensitive organometallic reagents requires petroleum-derived organic halides, which can be particularly problematic for large-scale synthesis. Moreover, the high basicity and nucleophilicity of alkyl organometallic reagents generally result in poor chemoselectivity and low functional group compatibility, inhibiting their synthetic applications. In addition, although alkyl boron reagents can achieve valuable chemoselectivities and have excellent functional group compatibility, they have been largely hampered by their challenging preparation. Consequently, the development of new alternatives for alkyl organometallic reagents in the allylation of alkyl carbanions is desired.

In recent years, hydrazones[16] can not only serve as nitrogen nucleophiles[17] but also play the role of ligands[18] in allylic alkylations. Furthermore, the reversal of electronic characteristics from simple hydrazones may facilitate the development of carbanion chemistry and create new opportunities for chemical transformations. Recently, Carreira and others[19] employed substituted hydrazones as formyl anion equivalents or stabilized alkyl carbanion equivalents (α-carbanions of carbonyl compounds) for allylic alkylation. However, the scope of both reactions was limited to specific substrates generated from formaldehyde or α-carbonyl aldehydes. Besides, these anion equivalents were relatively stable due to the presence of α-substituted imine or carbonyls. *A long-lasting challenge under such a context is if non-substituted hydrazones can serve as the unstabilized alkyl carbanion equivalents*. In pursuit of this protocol, our group recently disclosed that non-substituted hydrazones can serve as benzyl carbanion equivalents to undergo the addition or cross coupling reactions under the ruthenium, iron or nickel-catalyzed redox system.[20] Nevertheless, many other highly reactive alkyl organometallic reagent surrogates including alkyl aldehydes or ketones were less efficient via these methods. Herein, we report the umpolung of carbonyls[21] as efficient alkyl organometallic reagent surrogates for allylic alkylations via hydrazones intermediate (Scheme 1B). Such a strategy involves prevalent carbonyls (aryl or alkyl aldehydes and ketones) as renewable chemical feedstocks, and provides a catalytic alternative to the traditional use of alkyl organometallic reagents.



Scheme 1. Allylations of Non-Stabilized Alkyl Carbanions.

We initially began our studies by evaluating the coupling of benzaldehyde hydrazone **1ah** with allyl acetates (see the Supporting Information for more details). The base-free reaction did not lead to any *C*-allylated product (**4ah**, but-3-en-1-ylbenzene), while 18% yield of *N*-allylated product (**5**, *N*-allyl benzaldehyde hydrazone) and 80% yield of *N, N*-diallylated product (**6**, *N, N*-diallyl benzaldehyde hydrazone) were observed (entry 2), indicating that hydrazone **1ah** is prone to *N*-allylation in the absence of the base. Besides, no *C*-allylated or *N*-allylated products were detected in the absence of catalyst/ligand, suggesting that catalyst is indispensable for the allylation of hydrazones in this system (entry 3). We postulated that the combination of both the catalyst and the base mediates the deprotonation of hydrazones and directs the reaction of 2,3-diazaallyl anions **3** with π-allylpalladium to afford the *C*-allylated product **4ah**, *N*-allylated product **5** and *N, N*-diallylated product **6**. In such a context, the key challenge is to control the chemo- and regioselectivity to afford the *C*-allylation.

[a] Dr. D. Zhu,[+] Dr. L. Lv,[+] C.-C. Li, S. Ung, Dr. J. Gao, Prof. Dr. C.-J. Li
Department of Chemistry and FRQNT Center for Green Chemistry and Catalysis, McGill University, Montreal, QC, H3A 0B8, Canada
E-mail: cj.li@mcgill.ca
[+] These authors contributed equally to this work.

Supporting information for this article can be found under:

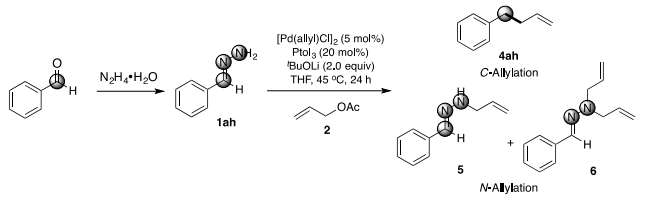
http://doi.org/10.1002/anie.201809112R1.

10.1002/anie.201809112

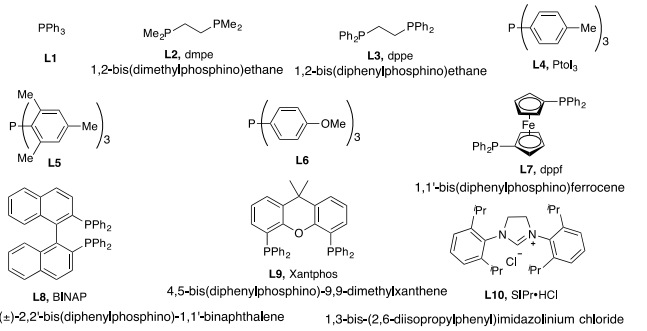
WILEY-VCH

COMMUNICATION

Table 1. Impact of Different Parameters on the Allylation of Hydrazones[a]



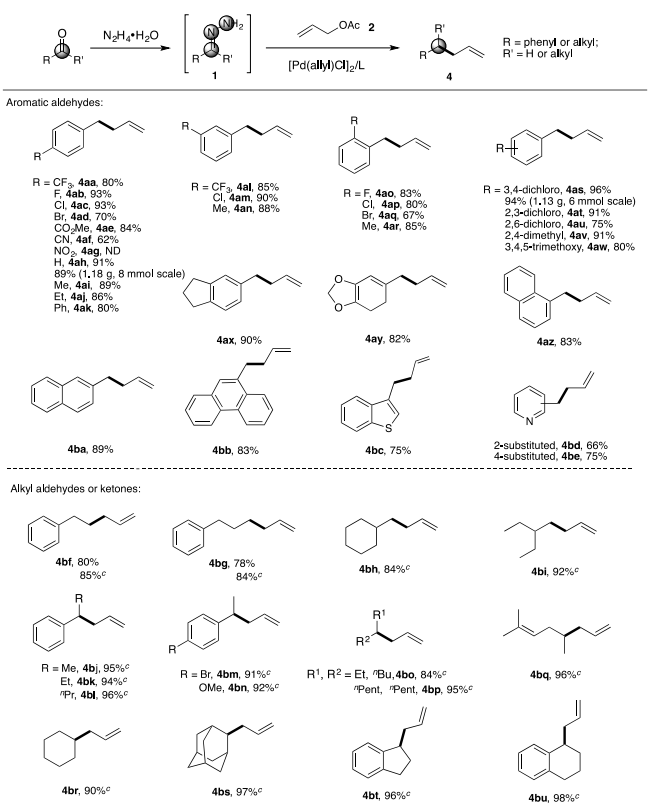
entry	variation from "standard conditions"	**4ah**:**5**:**6** (yield, %)
1	no change	98/1/0
2	no base	0/18/80
3	no $[Pd(allyl)Cl]_2$/$PtolI_3$	0/0/0
4	$Pd_2(dba)_3$ or $PdCl_2(PPh_3)_2$ instead of $[Pd(allyl)Cl]_2$	53/5/0 - 77/6/0
5	L1 instead of $PtolI_3$	90/1/0
6	L2, L3, L5-L9 instead of $PtolI_3$	9/58/0 - 22/60/3
7	L10 instead of $PtolI_3$	98/1/0.5
8	^{t}BuONa, ^{t}BuOK, DBU,K_3PO_4,K_3PO_4/CsF, Li_2CO_3, LiOH instead of ^{t}BuOLi	0/3/95 - 85/0/2
9	2-MeTHF, cyclopentyl methyl ether, 1,4-dioxane or diglyme instead of THF	68/7/4 - 44/1/1
10	RT instead of 45 °C	90/1/1



[a] Standard conditions: hydrazones (0.25 mmol, 1.25 M generated in situ from benzaldehyde and hydrazine), allyl acetate (0.20 mmol), $[Pd(allyl)Cl]_2$ (5 mol%), $PtolI_3$ (20 mol%), ^{t}BuOLi (2.0 equiv) in 1.0 mL THF at 45 °C for 24 h.

Surprisingly, reaction in the presence of 2.0 equiv of ^{t}BuOLi using a $[Pd(allyl)Cl]_2$/$PtolI_3$ (tri-*p*-tolylphosphine) catalytic system in THF (tetrahydrofuran) at 45 °C for 24 h provided the *C*-allylated product **4ah** in quantitative yield (98%), along with a high selectivity over the *N*-allylated product (**4ah**:**5** = 98:1) (entry 1). Other palladium catalysts including $Pd_2(dba)_3$ (dba: dibenzylideneacetone), $PdCl_2(PPh_3)_2$ gave moderate yields of **4ah** and a lower selectivity of allylic products (entry 4). Parallel experiments showed that with PPh_3 the reaction proceeded to afford 90% yield of *C*-allylated product **4ah** with a 90:1 selectivity over *N*-allylated product (entry 5); while reactions delivered unsatisfactory yields of **4ah** when dmpe, dppe, trismesitylphosphine, tri(*p*-methoxyphenyl) phosphine, dppf, BINAP and Xantphos were used as ligands (entry 6). It is also interesting to note that the carbene ligand SIPr·HCl could deliver similar results to $PtolI_3$ (entry 7). The choice of base was found to be crucial to the denitrogenation as well as the chemo- and regioselectivity: weak bases cannot trigger denitrogenation explaining why *N*-allylation or *N*, *N*-diallylation were the only products, while relatively strong bases could deliver satisfactory yields of *C*-allylated product **4ah** with a high selectivity over *N*-allylated product. While quantitative yield of **4ah** was observed with ^{t}BuOLi (entry 1), DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), K_3PO_4 or CsF could not give any of this product. It should be noted that 94%-95% yield of *N*, *N*-diallylated products **6** was formed in the presence of K_3PO_4 or K_3PO_4/CsF (entry 8). Other lithium salts such as Li_2CO_3 and LiOH, were also tested and no *C*-allylated product was detected, albeit with 30%-38% yield of *N*-allylated products and 36-60% yield of *N*, *N*-diallylated products. Moreover, a few green solvents, such as 2-methyltetrahydrofuran and cyclopentyl methyl ether, and other regular ether solvents such as 1,4-dioxane and diglyme, were also effective and delivered 37%-86% yields of *C*-allylated products (entry 9). Finally, the reaction could be performed at room temperature, with only a slightly decreased yield for the expected product (90%) (entry 10).

Table 2. Scope of Carbonyls[a,b]



[a] Reaction conditions: hydrazones (0.75 mmol, 1.25 M generated in situ from aldehydes or ketones and hydrazine), allyl acetate (0.6 mmol), $[Pd(allyl)Cl]_2$ (5 mol%), $PtolI_3$ (20 mol%), ^{t}BuOLi (2.0 equiv) in 3.0 mL THF at 45 °C for 24 h. [b] Isolated yield. [c] hydrazones (0.75 mmol), allyl acetate (0.6 mmol), $[Pd(allyl)Cl]_2$ (5 mol%), IPr·HCl (10 mol%), ^{t}BuOLi (2.2 equiv) in 3.0 mL THF at 45 °C for 24 h.

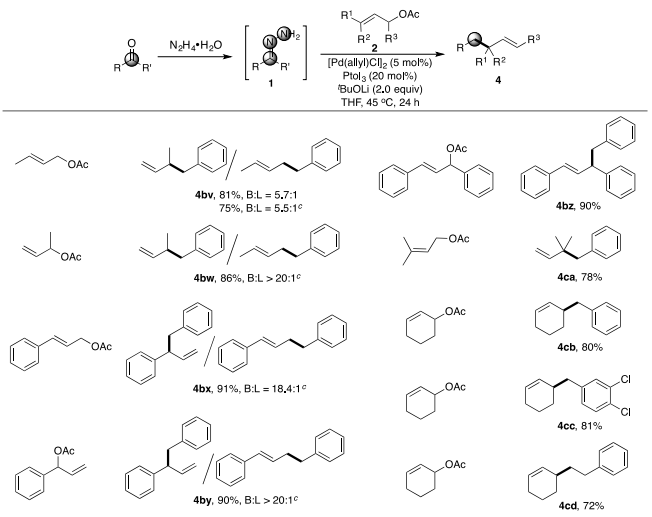
With the optimized conditions in hand, the substrate scope of allylation of hydrazones with allyl acetate was investigated in Table 2. In general, hydrazones bearing both electron-withdrawing and electron-donating substituted groups gave good to excellent yields, with the former giving higher yields. The reaction showed good functional group compatibility as well, as many functional groups such as trifluoromethyl, fluoro, chloro, cyano, methyl, ethyl, phenyl, methoxy and alkoxy substituents were all tolerated to give the corresponding products in high yields (**4aa-4ac**, **4af**, **4ah-4ay**). Some groups (such as bromo and ester substituents), which were not compatible with the traditional allylations of alkyl organometallic reagents, also worked well with our conditions (**4ad-4ae**). However, no desired product was observed for hydrazones bearing a strongly oxidizing nitro group (**4ag**). In addition to the good functional-group compatibility, *para*-, *meta*-, *ortho*-, or multi-substituted aromatic hydrazones were all tolerated in this system (**4aa-4ay**). Moreover, hydrazones prepared from polycyclic aromatic aldehydes such as 1-naphthaldehyde, 2-naphthaldehyde or phenanthrene-9-carbaldehyde delivered high yields of *C*-allylated products (**4az-4bb**). Hydrazones generated from heterocyclic aldehydes were then investigated under the standard conditions. Hydrazones prepared from benzo[*b*]thiophene-3-carbaldehyde, picolinaldehyde, or isonicotinaldehyde were all compatible with this system, affording the allylic product in 66%-75% yields (**4bc-4be**). To emphasize the synthetic potential of our methodology, a gram scale allylation of hydrazones was performed, giving products **4ac** and **4as** in 89% (1.18 g) and 94% yields (1.13 g), respectively.

To expand the scope of this methodology, we also studied the palladium-catalyzed allylation of hydrazones originated from alkyl aldehydes and ketones. Alkyl hydrazones generated from 2-phenylacetaldehyde and 3-phenylpropanal gave the desired products in 78%-80% yields using $PtolI_3$ as the ligand (**4bf-4bg**). However, this

10.1002/anie.201809112

system was unsuccessful with other alkyl aldehydes or ketones. After a quick screening of the reaction conditions, hydrazones prepared from alkyl aldehydes and ketones with allyl acetates occurred smoothly at 45 °C in THF, affording selectively *C*-allylated products in high to quantitative yield when IPr·HCl (1,3-bis(2,6-diisopropylphenyl)imidazolium chloride) was used as the ligand. Cyclohexanecarboxaldehyde hydrazone or 2-ethylbutanal hydrazone could afford 84%-92% yield of the desired products (**4bh-4bi**). Hydrazones originated from acetophenone and its derivatives also delivered high yields of the corresponding products (**4bj**, **4bm-4bn**). Besides, propiophenone hydrazone and 1-phenylbutan-1-one hydrazone were also effective in this system (**4bk-4bl**). In addition to aryl ketones, hydrazones elaborated from alkyl ketones including heptan-3-one, undecan-6-one, 5-methylhex-4-en-2-one and cyclohexanone, could successfully give the *C*-allylated products in 84%-96% yields with a high selectivity (**4bo-4br**). Other hydrazones generated from ketones with ring strain such as adamantan-2-one, 2,3-dihydro-1*H*-inden-1-one or 3,4-dihydronaphthalen-1(2*H*)-one reacted efficiently to give the desired allylic products in >95% yields (**4bs-4bu**).

Table 3. Scope of Allylic Acetates[a,b]

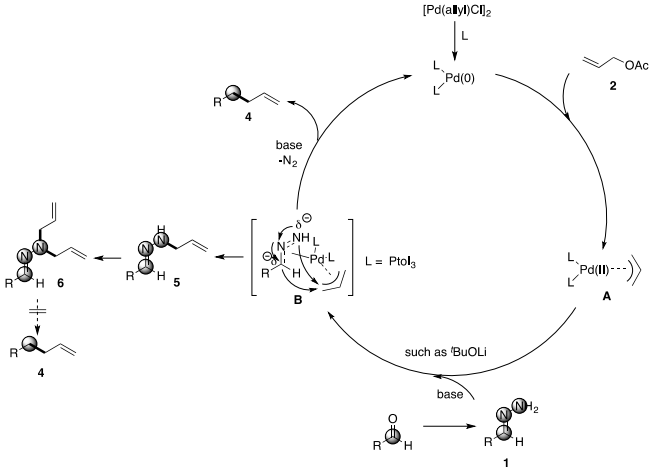


[a] Reaction conditions: hydrazones (0.75 mmol), allyl acetate (0.6 mmol), $[Pd(allyl)Cl]_2$ (5 mol%), $PtolI_3$ (20 mol%), ^{t}BuOLi (2.0 equiv) in 3.0 mL THF at 45 °C for 24 h. [b] Isolated yield. [c] hydrazones (0.75 mmol), allyl acetate (0.6 mmol), $[Pd(allyl)Cl]_2$ (5 mol%), SIPr·HCl (10 mol%), ^{t}BuOLi (2.2 equiv) in 3.0 mL THF at 45 °C for 24 h.

Subsequently, the allyl acetate substrate scope was investigated in Table 3. The transformations delivered the branched allylic products with excellent yields (**4bv-4cd**) and high B/L ratio (branched : linear up to > 20:1) (**4bw-4by**), likely due to the steric effect associated with the 3,3'-elimination in the regiochemistry-determining step analogous to Morken's work[6d-6e] (see the Supporting Information for more details). Besides, coupling of hydrazones with 2-cyclohexenyl acetate could also deliver the corresponding products in 72%-81% yields (**4cb-4cd**).

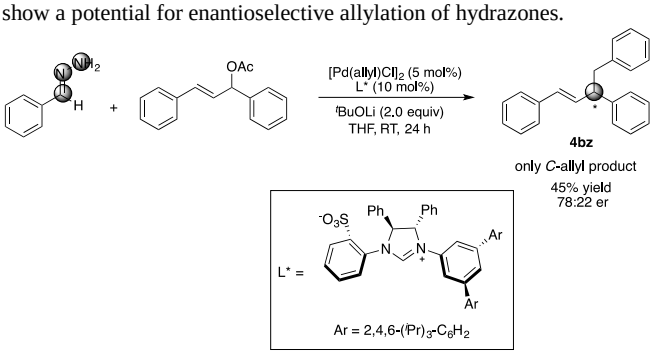
The excellent functional group tolerance highlights the great potential of this reaction for the transformation of natural aldehydes and their derivatives (see the Supporting Information for more details). Under the standard conditions, hydrazones originated from 4-hydroxyaldehyde derivatives (methyl, benzyl or allyl 4-hydroxyaldehyde) gave *C*-allylated products in 84%, 86% and 84% yields, respectively (**4ce-4cg**). Besides, Veratraldehyde (methyl Vanillin) could efficiently afford the *C*-allylated product (4-(but-3-en-1-yl)-1,2-dimethoxybenzene) in high yield (**4ch**). Likewise, the conjugation of azaallyl anions with an olefin was also tolerated and gave the *C*-allylated product. Allylation of the hydrazone elaborated from cinnamaldehyde afforded a 68% yield with a mixture of branched and linear products (B:L (**4ci**:**4ci'**) = 1.7:1).

Based on the mechanistic studies (see the Supporting Information for more details) and previous literatures,[22] a tentative mechanism of the palladium-catalyzed allylation of hydrazones is proposed in Scheme 2. Initially, allyl acetates **2** and Pd (0)/phosphine complex, derived from $[Pd(allyl)Cl]_2$ and tri-*p*-tolylphosphine, generate the π-allylpalladium complex **A** via oxidative addition. Then, after deprotonation in the presence of the base (^{t}BuOLi), hydrazones **1** ligates to complex **A** forming 2,3-diazaallyl anions of benzaldehyde hydrazone (complex **B**). Subsequently, 2,3-diazaallyl anions attack the π-allylpalladium complex to afford the corresponding allylic products (*C*-allylated product **4** or *N*-allylated product **5** or **6**) through reductive elimination in the presence of base and regenerates the Pd (0)/phosphine. High yields of **4** and high chemo- and regioselectivity towards *C*-allylated products **4** can only be obtained in the presence of 2.0 equiv of ^{t}BuOLi.



Scheme 2. A Tentative Mechanism.

Finally, preliminary asymmetric allylation studies were carried out. When the chiral carbene ligand generated from a sulfonate-bearing imidazolinium salt with a 3,5-diaryl-substituted phenyl moiety (L*) was used, **4bz** was obtained in 45% yield with 78:22 enantiomeric ratio (e.r.) at room temperature (Scheme 3). The preliminary investigations thus show a potential for enantioselective allylation of hydrazones.



Scheme 3. Preliminary Investigations on Asymmetric Allylation of Hydrazones

In summary, we have developed a direct highly chemo- and regioselective *C*-allylation of non-substituted hydrazones enabled by palladium catalyst. Highlighted features of this methodology are: (a) effective for a wide variety of hydrazones originated not only from aryl aldehydes, but also alkyl aldehydes and ketones, (b) umpolung of carbonyls as highly reactive alkyl organometallic reagent surrogates for allylic alkylation, (c) the use of only a catalytic amount of both metal and ligand, (d) the high yields and ease to scale up, (e) the compatibility with a wide range of functional groups while maintaining a high chemo- and regioselectivity of *C*-allylation. With all those characteristics, this umpolung reaction is expected to complement the palladium-catalyzed methods using stabilized nucleophiles and it provides with a novel catalytic alternative to the traditional use of highly reactive alkyl organometallic reagents. It is very likely that more strategies using hydrazones as unstabilized alkyl carbanion equivalents for other cross-coupling reactions will emerge in the future.

Acknowledgements

The authors acknowledge the Canada Research Chair Foundation, the CFI, FQRNT Center for Green Chemistry and Catalysis, NSERC, and McGill University for the support of our research. The authors also thank Shanghai Institute of Organic Chemistry (SIOC) for supporting a postdoctoral fellowship to D. Zhu.

Conflict of interest

The authors declare no conflict of interest.

Keywords: carbonyl • hydrazone • alkyl organometallic reagent • allylic alklation • palladium catalysis

[1] For selected review, see: (a) B. M. Trost, *Chem. Rev*. **1996**, *96*, 395-422; (b) B. M. Trost, M. R. Machacek, A. Aponick, *Acc. Chem. Res*. **2006**, *39*, 747-760; (c) Z. Lu, S. Ma, *Angew. Chem. Int. Ed*. **2008**, *47*, 258-297; (d) M. Diéguez, O. Pàmies, *Acc. Chem. Res*. **2010**, *43*, 312-322; (e) J. D. Weaver, A. Recio III, A. J. Grenning, J. A. Tunge, *Chem. Rev*. **2011**, *111*, 1846-1913; (f) L. Milhau, P. J. Guiry, *Top. Organomet. Chem*. **2012**, *38*, 95-154.

[2] For selected applications in organic synthesis, see: (a) M. Ernst, G. Helmchen, *Angew. Chem. Int. Ed*. **2002**, *41*, 4054-4056; (b) B. M. Trost, M. L. Crawley, *Chem. Rev*. **2003**, *103*, 2921-2943; (c) J. A. Enquist Jr, B. M. Stoltz, *Nature* **2008**, *453*, 1228-1231; (d) A. D. Huters, E. D. Styduhar, N. K. Garg, *Angew. Chem. Int. Ed*. **2012**, *51*, 3758-3765; (e) Y. Liu, S. -J. Han, W. -B. Liu, B. M. Stoltz, *Acc. Chem. Res*. **2015**, *48*, 740-751.

[3] For selected other representative metal-catalyzed allylation, see: Ir: (a) J. F. Hartwig, L. M. Stanley, *Acc. Chem. Res*. **2010**, *43*, 1461-1475; (b) S. Krautwald, D. Sarlah, M. A. Schafroth, E. M. Carreira, *Science* **2013**, *340*, 1065-1068; (c) C. -X. Zhuo, C. Zheng, S. -L. You, *Acc. Chem. Res*. **2014**, *47*, 2558-2573; (d) X. Huo, R. He, X. Zhang, W. Zhang, *J. Am. Chem. Soc*. **2016**, *138*, 11093-11096; Ni: (e) Y. Yatsumonji, Y. Ishida, A. Tsubouchi, T. Takeda, *Org. Lett.* **2007**, *9*, 4603-4606; (f) R. Matsubara, T. F. Jamison, *J. Am. Chem. Soc*. **2010**, *132*, 6880-6881; (g) Y. Kita, R. D. Kavthe, H. Oda, K. Mashima, *Angew. Chem. Int. Ed*. **2016**, *55*, 1098-1101.

[4] For selected palladium-catalyzed allylation of α-carbanions of carbonyl compounds, see: (a) X. -X. Yan, C. -G. Liang, Y. Zhang, W. Hong, B. -X. Cao, L. -X. Dai, X. -L. Hou, *Angew. Chem. Int. Ed*. **2005**, *44*, 6544-6546; (b) I. Ibrahem, A. Córdova, *Angew. Chem. Int. Ed*. **2006**, *45*, 1952-1956; (c) M. Braun, T. Meier, *Angew. Chem. Int. Ed*. **2006**, *45*, 6952-6955; (d) S. Mukherjee, B. J. List, *J. Am. Chem. Soc*. **2007**, *129*, 11336-11337; (e) X. Zhao, D. Liu, H. Guo, Y. Liu, W. Zhang, *J. Am. Chem. Soc*. **2011**, *133*, 19354-19357; (f) D. C. Behenna, Y. Liu, T. Yurino, J. Kim, D. E. White, S. C. Virgil, B. M. Stoltz, *Nat. Chem*. **2011**, *4*, 130-133; (g) J. D. St. Denis, Z. He, A. K. Yudin, *Org. Biomol. Chem.* **2012**, *10*, 7900-7902; (h) Z. -L. Tao, W. -Q. Zhang, D. -F. Chen, A. Adele, L. -Z. Gong, *J. Am. Chem. Soc*. **2013**, *135*, 9255-9258; (i) K. Ohmatsu, M. Ito, T. Kunieda, T. Ooi, *J. Am. Chem. Soc*. **2013**, *135*, 590-593; (j) X. Huo, G. Yang, D. Liu, Y. Liu, I. D. Gridnev, W. Zhang, *Angew. Chem. Int. Ed*. **2014**, *53*, 6776-6780; (k) J. M. Howell, W. Liu, A. J. Young, M. C. White, *J. Am. Chem. Soc*. **2014**, *136*, 5750-5754; (l) H. Zhou, L. Zhang, C. Xu, S. Luo, *Angew. Chem. Int. Ed*. **2015**, *54*, 12645-12648.

[5] For selected palladium-catalyzed allylation of electron-rich substrates, see: (a) S. -L. You, X. -Z. Zhu, Y. -M. Luo, X. -L. Hou, L. -X. Dai, *J. Am. Chem. Soc*. **2001**, *123*, 7471-7472; (b) S. Shekhar, B. Trantow, A. Leitner, J. F. Hartwig, *J. Am. Chem. Soc*. **2006**, *128*, 11770-11771; (c) B. J. Stokes, S. M. Opra, M. S. Sigman, *J. Am. Chem. Soc*. **2012**, *134*, 11408-11411; (d) A. Sharma, J. F. Hartwig, *J. Am. Chem. Soc*. **2013**, *135*, 17983-17989; (e) T. -S. Mei, H. H. Patel, M. S. Sigamn, *Nature* **2014**, *508*, 340-344; (f) Q. Zhao, C. -X. Zhuo, S. -L. You, *RSC Adv.*, **2014**, *4*, 10875-10878; (g) R. -D. Gao, Q. -L. Xu, L. -X. Dai, S. -L. You, *Org. Biomol. Chem.* **2016**, *14*, 8044-8046.

[6] (a) A. Misale, S. Niyomchon, M. Luparia, N. Maulide, *Angew. Chem. Int. Ed*. **2014**, *53*, 7068-7073; (b) I. Stary, P. Kocovsky, *J. Am. Chem. Soc*. **1989**, *111*, 4981-4982; (c) B. M. Trost, D. A. Thaisrivongs, *J. Am. Chem. Soc*. **2008**, *130*, 14092-14093; (d) P. Zhang, L. A. Brozek, J. P. Morken, *J. Am. Chem. Soc*. **2010**, *132*, 10686-10688; (e) L. A. Brozek, M. J. Ardolino, J. P. Morken, *J. Am. Chem. Soc*. **2011**, *133*, 16778-16781.

[7] C. Chuit, H. Felkin, C. Frajerman, G. Roussi, G. Swierczewski, *Chem. Comm*. **1968**, 1604-1605.

[8] C. C. Tseng, S. D. Paisley, H. L. Goering, *J. Org. Chem*. **1986**, *51*, 2884-2891.

[9] N. M. Heron, J. A. Adams, A. H. Hoveyda, *J. Am. Chem. Soc*. **1997**, *119*, 6205-6206.

[10] (a) S. R. Harutyunyan, T. Den Hartog, K. Geurts, A. J. Minnaard, B. L. Feringa, *Chem. Rev*. **2008**, *108*, 2824-2852; (b) M. Giannerini, M. Fañanás-Mastral, B. L. Feringa, *J. Am. Chem. Soc*. **2012**, *134*, 4108-4111.

[11] (a) W. Lölsberg, S. Ye, H. -G. Schmalz, *Adv. Synth. Catal*. **2010**, *352*, 2023-2031; (b) O. Jackowski, A. Alexakis, *Angew. Chem. Int. Ed*. **2010**, *49*, 3346-3350; (c) A. M. Lauer, F. Mahmud, J. Wu, *J. Am. Chem. Soc*. **2011**, *133*, 9119-9123.

[12] (a) H. Malda, A. W. Van Zijl, L. A. Arnold, B. L. Feringa, *Org. Lett*. **2001**, *3*, 1169-1171; (b) M. A. Kacprzynski, A. H. Hoveyda, *J. Am. Chem. Soc*. **2004**, *126*, 10676-10681; (c) M. A. Kacprzynski, T. L. May, S. A. Kazane, A. H. Hoveyda, *Angew. Chem*. **2007**, *119*, 4638-4642; (d) S. Son, G. C. Fu, *J. Am. Chem. Soc*. **2008**, *130*, 2756-2757.

[13] M. Fañanás-Mastral, M. Pérez, P. H. Bos, A. Rudolph, S. R. Harutyunyan, B. L. Feringa, *Angew. Chem. Int. Ed*. **2012**, *51*, 1922-1925.

[14] R. Millet, T. Bernardez, L. Palais, A. Alexakis, *Tetrahedron Lett*. **2009**, *50*, 3474-3477.

[15] H. Z. You, E. Rideau, M. Sidera, S. P. Fletcher, *Nature* **2015**, *517*, 351-355.

[16] (a) J. E. Baldwin, J. C. Bottaro, J. N. Kolhe, R. M. Adlington, *J. Chem. Soc., Chem, Commun*. **1984**, 22-23; (b) J. E. Baldwin, R. M. Adlington, J. C. Bottaro, J. N. Kolhe, I. M. Newington, M. W. D. Perry, *Tetrahedron* **1986**, *42*, 4235-4246.

[17] For selected examples of substituted hydrazones as nitrogen nucleophiles in allylic allylation, see: (a) A. M. Johns, Z. Liu, J. F. Hartwig, *Angew. Chem. Int. Ed*. **2007**, *46*, 7259-7261; (b) B. Lu, B. Feng, H. Ye, J. -R. Chen, W. -J. Xiao, *Org. Lett*. **2018**, *20*, 3473-3476.

[18] For selected examples of hydrazones as ligands in palladium-catalyzed allylic allylation, see: (a) T. Mino, M. Shiotsuki, N. Yamamoto, T. Suenaga, M. Sakamoto, T. Fujita, M. Yamashita, *J. Org. Chem*. **2001**, *66*, 1795-1797; (b) T. Mino, H. Segawa, M. Yamashita, *J. Organomet. Chem*. **2004**, *689*, 2833-2836.

[19]. (a) S. Breitler, E. M. Carreira, *J. Am. Chem. Soc*. **2015**, *137*, 5296-5299; (b) EI. H. El Mamouni, M. Cattoen, M. Cordier, J. Cossy, S. Arseniyadis, H. Ilitki, L. El Kaïm, *Chem. Commun*. **2016**, *52*, 14490-14493.

[20] (a) H. Wang, X. -J. Dai, C. -J. Li, *Nat. Chem*. **2017**, *9*, 374-378; (b) N. Chen, X. -J. Dai, H. Wang, C. -J. Li, *Angew. Chem. Int. Ed*. **2017**, *56*, 6260-6263; (c) X. -J. Dai, H. Wang, C. -J. Li, *Angew. Chem. Int. Ed*. **2017**, *56*, 6302-6306; (d) W. Wei, X .-J. Dai, H. Wang, C. -C. Li, X. Yang, C. -J. Li, *Chem. Sci.* **2017**, *8*, 8193-8197; (e) J. Tang, L. Lv, X. -J. Dai, C. -C. Li, L. Li, C. -J. Li, *Chem. Comm*. **2018**, *54*, 1750-1753; (f) L. Lv, D. Zhu, J. Tang, Z. Qiu, C. -C. Li, J. Gao, C. -J. Li, *ACS Catal.* **2018**, *8*, 4622-4627; (g) C. -C. Li, X. -J. Dai, H. Wang, D. Zhu, J. Gao, C. -J. Li, *Org. Lett*. **2018**, *20*, 3801-3805.

[21] For selected examples of Umpolung allylation, see: (a) J. Liu, C. -G. Cao, H. -B. Sun, X. Zhang, D. Niu, *J. Am. Chem. Soc*. **2016**, *138*, 13103-13106; (b) K. Yao, D. Liu, Q. Yuan, T. Imamoto, Y. Liu, W. Zhang, *Org. Lett*. **2016**, *18*, 6296-6299.

[22] For recent reports on mechanistic studies, see: (a) M. Kollmar, B. Goldfuss, M. Reggelin, F. Rominger, G. Helmchen, *Chem. Eur. J.* **2001**, *7*, 4913-4927; (b) I. D. G. Watson, A. K. Yudin, *J. Am. Chem. Soc.* **2005**, *127*, 17516-17529; (c) C. Amatore, A. Jutand, L. Mensah, G. Meyer, J. C. Fiaud, J. -Y. Legros, *Eur. J. Org. Chem.* **2006**, 1185-1192; (d) O. Piechaczyk, C. Thoumazet, Y. Jean, P. Le Floch, *J. Am. Chem. Soc.* **2006**, *128*, 14306-14317; (e) M. Z. De Luliis, L. D. G. Watson, A. K. Yudin, R. H. Morris, *Can. J. Chem.* **2009**, *87*, 54-62.

10.1002/anie.201809112

WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

Text for Table of Contents

((Insert TOC Graphic here))

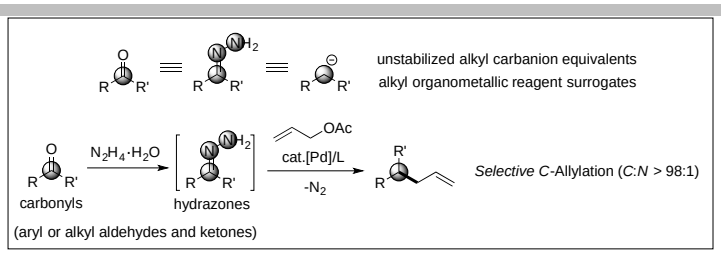
*Author(s), Corresponding Author(s)**

Page No. – Page No.

Title

Layout 2:

COMMUNICATION



Umpolung of Carbonyls in Allylic Alklation: A direct palladium-catalyzed highly chemo- and regioselective *C*-allylation of hydrazones was developed using umpolung carbonyls as a source of unstabilized alkyl carbanions and surrogates of highly reactive alkyl organometallic reagents, with a catalytic amount of both metal and ligand, high yields, ease to scale up, wide substrate scopes and great functional group compatibility**.**

*Dianhu Zhu, Leiyang Lv, Chen-Chen Li, Sosthene Ung, Jian Gao and Chao-Jun Li**

Page No. – Page No.

Umpolung of Carbonyl Groups as Alkyl Organometallic Reagent Surrogates for Palladium-Catalyzed Allylic Alkylation