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Introducing Unactivated Acyclic Internal Aliphatic Olefins in Cobalt Catalyzed Allylic Selective Dehydrogenative Heck Reaction

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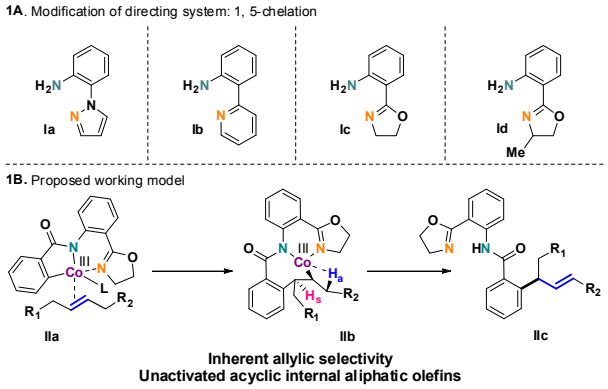
Abstract: Unactivated acyclic internal aliphatic olefins are often found unreactive in conventional alkenylation reactions. Addressing this problem, a cobalt catalyzed allylic selective dehydrogenative Heck reaction with internal aliphatic olefins has been developed. The method is highly regio- and stereoselective, the conditions are mild and can tolerate a wide variety of functional groups. Remarkably, both internal and terminal aliphatic olefins can be employed, thereby significantly expanding the scope of alkenylation chemistry with aliphatic olefins.

Introduction:

Selective incorporation of unactivated aliphatic olefins into arenes is a highly sought-after transformation in modern Heck chemistry.[1] The ubiquity and synthetic potential of aliphatic olefins and α-olefins, have inspired significant development in recent times.[2] An existing problem of this methodology, however, is the inertness of internal aliphatic olefins. This could be attributed to a number of factors such as inappropriate coordination or sensitivity towards the enhanced steric environment in the carbometallation step.[3] To solve this problem, discovery and development of new catalysts seemed essential. Here we report a method that overcome these limitations and successfully introduced internal aliphatic olefins in a highly regio- and stereoselective manner.

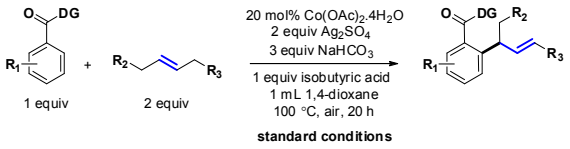


Scheme 1. Evaluation of directing groups with internal aliphatic olefins

Our recent studies suggested that an inexpensive and readily available cobalt catalyst could facilitate an allylic selective Heck-type reaction with a variety of terminal aliphatic olefins.[4] The unorthodox allylic selectivity was attributed to a flexible framework consisting of a *bis*-chelating directing scaffold, that placed the metal suitably to generate the allylic product. An attempt to extend this reaction to internal aliphatic olefins, however remained unsuccessful as competitive reductive elimination predominated.[5] We hypothesized that a structural modification of the 5,7-membered fused metalacycle intermediate (such as **IIb**) could suppress the annulation pathway. As a consequence, unbiased internal aliphatic olefins could be selectively included (Scheme 1B).

This hypothesis led to the synthesis and evaluation of several 1,5-bis chelating systems with attached pyrazole, pyridine and dihydrooxazole moiety. Out of this selection of directing groups, 2-(4,5-dihydrooxazol-2-yl)aniline (**Ic**, Scheme 1A), first developed by the Yu group, showed promising reactivity with commercially available cobalt catalysts.[6] Optimization of reaction parameters and inclusion of aliphatic acid additives considerably increased the efficiency of the method (Table 1). Under the optimized conditions,

Table 1. Optimization of several reaction parameters



Entry	Catalyst	Oxidant	Solvent	Yield
1	$Co(OAc)_2.4H_2O$	Ag_2SO_4	DCE	19
2	$Co(OAc)_2.4H_2O$	Ag_2SO_4	1,4-dioxane	38
3	$Co(OAc)_2.4H_2O$	Ag_2CO_3	1,4-dioxane	35
4	$Co(OAc)_2.4H_2O$	$PhI(OAc)_2$	1,4-dioxane	19
5	$Co(OAc)_2.4H_2O$	Ag_2SO_4	1,4-dioxane	90%[a]
6	$Co(acac)_2$	Ag_2SO_4	1,4-dioxane	51%
7	$CoBr_2$	Ag_2SO_4	1,4-dioxane	56%

[a]with 1 equiv. isobutyric acid additive and 3 equiv. $NaHCO_3$ base.

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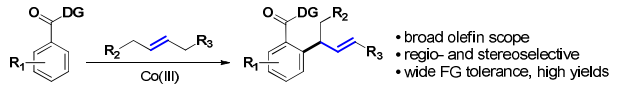
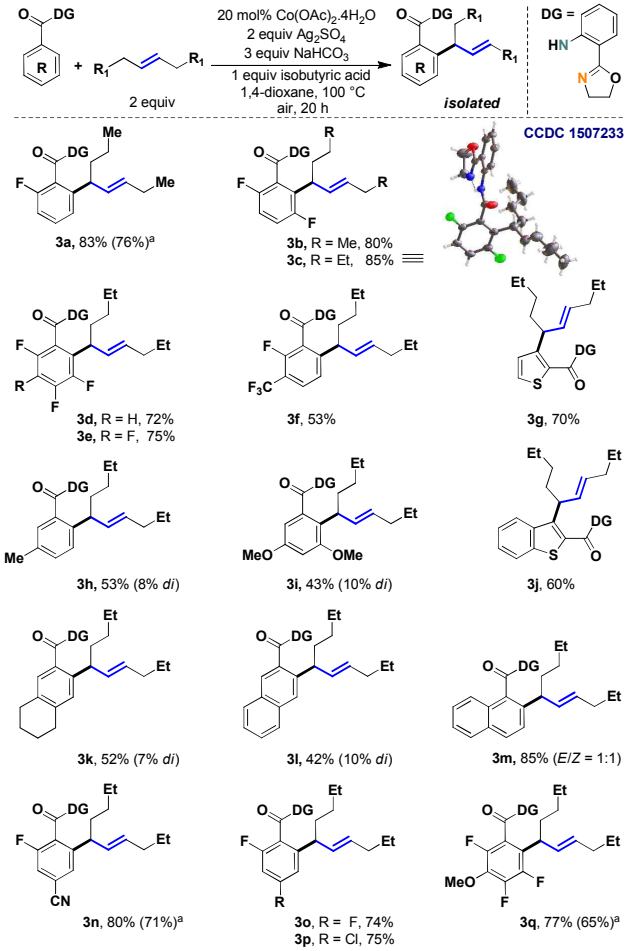
completely *allylic* selective alkenylated products could be obtained in high synthetic yields with very high diastereomeric ratios (Scheme 2).



Scheme 2. Introducing acyclic internal aliphatic olefins in dehydrogenative Heck chemistry

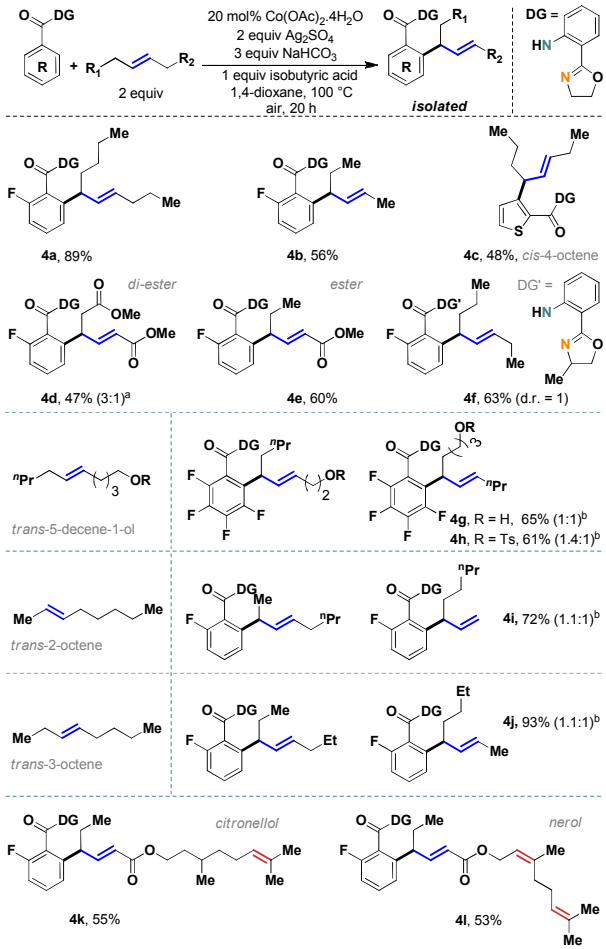
Results and discussion:

We began to study the scope of the reaction with *trans*-4-octene as the model olefin. These olefins have been historically proven difficult substrates for any Heck-type transformations and Fujiwara-Moritani reactions.[7] In the absence of electronic bias, the migratory insertion step is less facile and the methods often suffer from poor reaction rates. Even if the metal could bind with the olefin effectively, the carbometallation intermediate (**IIb**) might lead to a deleterious mixture of styrenyl/allylic products.[8] In the present system, however, the affiliation of the 1,5 chelating directing scaffold and the cobalt catalyst proved to be inherently allylic selective. [9], [10] Although the origin of this selectivity is yet to be fully established, given the thermodynamic non-preference of *allylic* isomers (vs. *styrenyl*), this observation demanded a more detailed evaluation of scope of the reaction.



Scheme 3. Allylic selective alkenylation with unactivated acyclic internal aliphatic olefins. [a]Yields with 10 mol% Co.

Therefore, we tested different benzoic acid derivatives under standard conditions (Scheme 3). It was observed that the reaction was quite general as both electron donating as well as electron withdrawing substituents could be tolerated at the *ortho*-, *meta*- or *para*-positions of the arene ring. Even multiple fluoro groups did not affect the efficiency of the method (**3b**-**3e** and **3q**). Among the synthesized compounds, entry **3c** was characterized through X-ray crystallography, thereby unambiguously assigning the *trans*-geometry of the *α*-branched internal allylarene product. Different functional groups such as -CN, -Cl, -OMe were well suited (**3n**, **3p** and **3q**; 75-80%). When both the *ortho*- positions were unsubstituted, some amount of *di*-allylation (7-10%) was observed, which could be easily purified through column chromatography. For substrates with moderate yields (**3i** and **3l**), the unreacted starting materials were recovered in considerable amount. Heteroaromatic benzoic acids such as thiophene (**3g**, 70%) and benzothiophene (**3j**, 60%) carboxylic acids were also found to be useful substrates. Interestingly a chiral center has been generated in all these cases; thus a future development of an asymmetric variant of the method could be envisaged.



Scheme 4. Evaluation of unactivated acyclic internal aliphatic olefins. [a]another isomer can be detected in minor amount; [b]regioisomeric ratios are mentioned in parenthesis.

The scope of the method was evaluated further with different internal aliphatic olefins (Scheme 4). As expected, a higher homologue, *trans*-5-decene was found to be equally reactive (**4a**,

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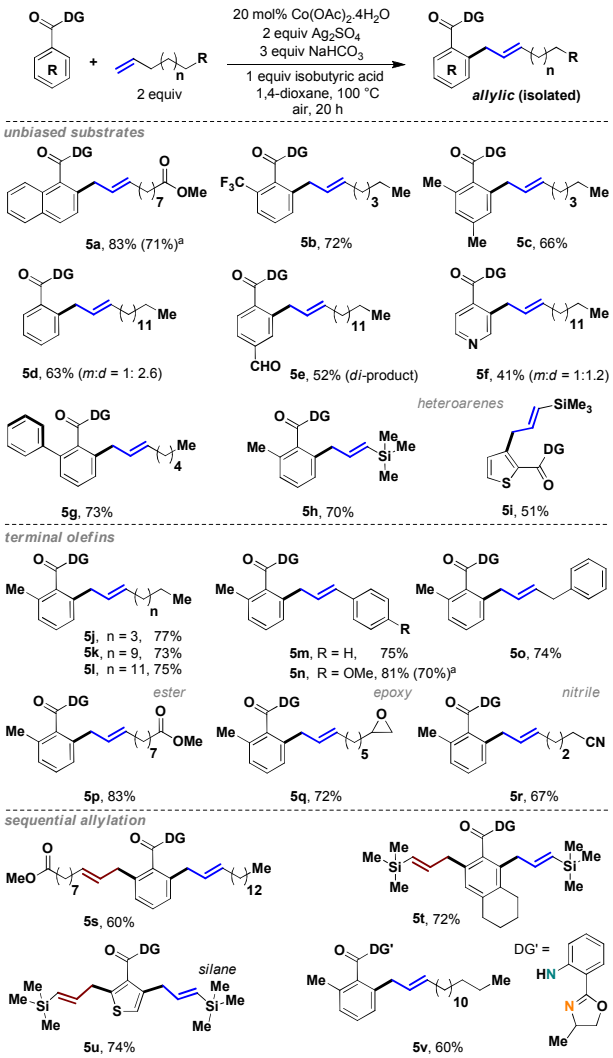
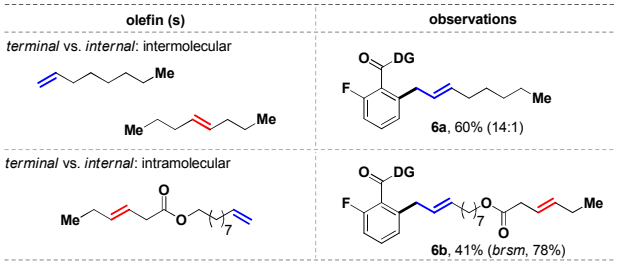
89%). Although we observed a slight erosion of efficiency with *trans*-3-hexene (**4b**), that might be attributed to the volatility of the olefin substrate. A free alcohol containing olefin could be successfully employed without oxidation of the alcohol functional group (**4g**, 65%). Other unsymmetrical internal olefins were also useful in this reaction (entries **4g**-**4l**). An internal allyl ester was particularly interesting as regioselective allylation was observed in 8:1 ratio (**4e**, 60%). Although in principle, two allyl isomers are possible, the conjugation with the carbonyl group determined the geometry of the major allyl isomer. A similar reactivity pattern was observed with internal olefins derived from naturally occurring citronellol (**4l**) and nerol (**4m**), which had additional tri-substituted double bonds. Unfortunately despite our best efforts, *cis*-olefins proved to be difficult substrates (**4c**, 48%). Even prolonged reaction time failed to improve the synthetic yield to a considerable extent. Nevertheless, in perspective of the documented difficulties with internal aliphatic olefins, these studies seemed very encouraging.



Scheme 5. Allylic selectivity with terminal aliphatic olefins. [a]Yields with 10 mol% Co.

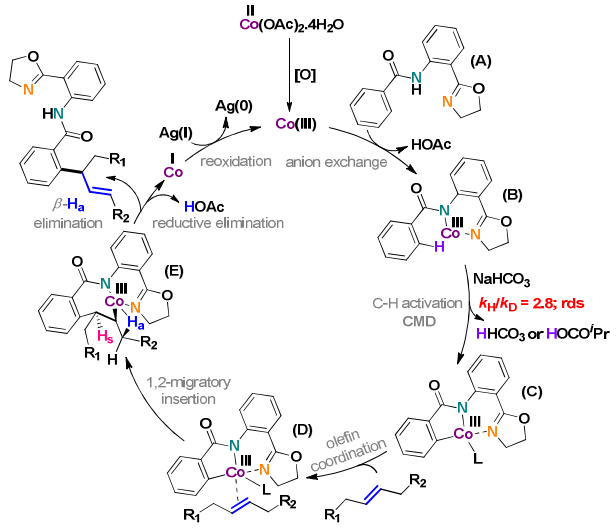
To gain additional insight as to whether this reactivity was internal specific, we decided to assess terminal aliphatic olefins as well (Scheme 5). We were pleased to observe that a wide variety of terminal alkenes could be incorporated with excellent yields and complete allylic selectivity. Simple benzoic acids as well as heteroaromatic acids, without any bias, were useful substrates thereby significantly expanding the scope of allylation with aliphatic olefins (**5a**-**5i**). Additionally, sequential allylation could be performed with equal ease (**5s**-**5u**).[11]

We next decided to study comparative reactivity of different aliphatic olefins (Scheme 6). An intermolecular competition experiment revealed that 1-octene could react preferentially in 14:1 ratio over *trans*-4-octene (**6a**, 60%). Similarly, a substrate with both terminal and internal olefins reacted exclusively at the terminal site, while internal olefin remained completely unreacted (**6b**). Kinetic studies further showed that a *trans*-olefin reacts 2.5 times faster than the *cis*-isomer, which partially explained the apparent lower reactivity of a *cis*-olefin under the standard conditions.



Scheme 6. Competition experiments with aliphatic olefins

A plausible mechanism has been depicted in Scheme 7. The reaction was thought to be initiated by an *in-situ* generated Co(III) species under aerobic conditions. C–H activation (**C**), olefin coordination (**D**), and subsequent migratory insertion lead to a unique seven-membered intermediate (**E**), stability of which was very crucial for progress of the reaction. In all probability, the geometry of this particular intermediate determined the regioselective outcome of the method.



Scheme 7. Plausible mechanism for allylic selective alkenylation with internal aliphatic olefins

It was found that the aliphatic acid additives had a profound influence on the rate enhancement. In sharp contrast, omitting $NaHCO_3$ slightly altered the rate of the reaction (Scheme 8). This could be justified by considering the superiority of aliphatic

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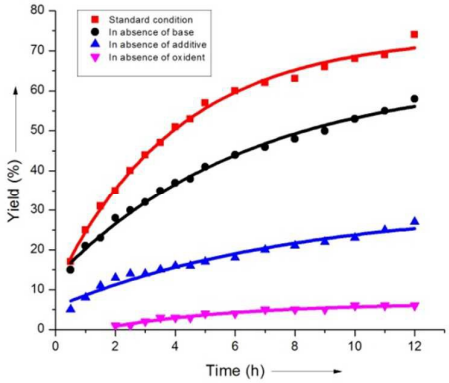
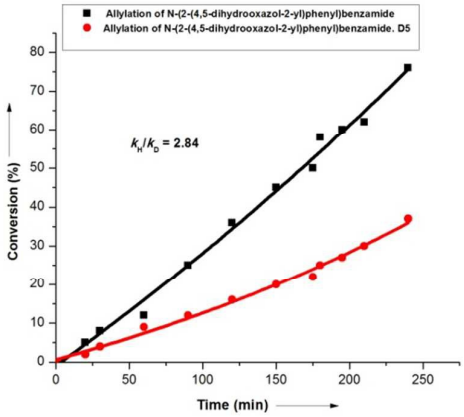
carboxylate ($^{i}PrCO_2Na$) as the proton abstracting agent in the C–H activation step (**B**), thus clearly indicating a concerted metallation-deprotonation or CMD-type pathway to be operative.



Scheme 8. Kinetic investigation of reaction components

Interestingly, labeling studies revealed k_H/k_D value of 2.8, thereby suggesting C–H activation as the rate determining step (r.d.s.) of the overall transformation (Scheme 9). This observation was supported further by the fact that both internal and terminal olefins could react at nearly same rate in parallel experiments (see supporting information).



Scheme 9. Determination of kinetic isotope effect

Conclusions:

In summary, we have developed a cobalt catalyzed allylic selective alkenylation with unactivated internal aliphatic olefins. The excellent regio- and stereoselectivity, broad scope, and high synthetic yields are some of the noteworthy features of the present method. Remarkably, a variety of acyclic internal aliphatic olefins were successfully incorporated. Development of a related asymmetric transformation and detailed mechanistic investigations are presently underway in our laboratory.

Acknowledgement

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References

[1]. For selected references on Heck reactions with aliphatic olefins, see: a) J. H. Delcamp, A. P. Brucks and M. C. White, *J. Am. Chem. Soc.*, 2008, **130**, 11270; b) E. W. Werner and M. S. Sigman, *J. Am. Chem. Soc.*, 2010, **132**, 13981; c) E. W. Werner and M. S. Sigman, *J. Am. Chem. Soc.*, 2011, **133**, 9692; d) A. Deb and D. Maiti, *Eur. J. Org. Chem.*, **2017**, 1239.

[2]. For selective alkenylation with aliphatic olefins, see: a) Y. Lu, D.-H. Wang, K. M. Engle and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 5916; b) A. S. Tsai, M. Brasse, R. G. Bergman and J. A. Ellman, *Org. Lett.*, 2011, **13**, 540; c) X. Li, X. Gong, M. Zhao, G. Song, J. Deng and X. Li, *Org. Lett.*, 2011, **13**, 5808; d) R. Matsubara, A. C. Gutierrez and T. F. Jamison, *J. Am. Chem. Soc.*, 2011, **133**, 19020; e) L. Qin, X. Ren, Y. Lu, Y. Li and J. Zhou, *Angew. Chem. Int. Ed.*, 2012, **51**, 5915; f) C. Zheng, D. Wang and S. S. Stahl, *J. Am. Chem. Soc.*, 2012, **134**, 16496; g) C. S. Sevov and J. F. Hartwig, *J. Am. Chem. Soc.*, 2014, **136**, 10625; h) A. Deb, S. Bag, R. Kancherla and D. Maiti, *J. Am. Chem. Soc.*, 2014, **136**, 13602; i) X. Xue, J. Xu, L. Zhang, C. Xu, Y. Pan, L. Xu, H. Li and W. Zhang, *Adv. Synth. Catal.*, 2016, **358**, 573.

[3]. For significant development of Heck chemistry with aliphatic alkenols and cyclic olefins, see: a) E. W. Werner, T.-S. Mei, A. J. Burckle and M. S. Sigman, *Science*, 2012, **338**, 1455; b) T.-S. Mei, E. W. Werner, A. J. Burckle and M. S. Sigman, *J. Am. Chem. Soc.*, 2013, **135**, 6830; c) L. Xu, M. J. Hilton, X. Zhang, P.-O. Norrby, Y.-D. Wu, M. S. Sigman and O. Wiest, *J. Am. Chem. Soc.*, 2014, **136**, 1960; d) T.-S. Mei, H. H. Patel and M. S. Sigman, *Nature*, 2014, **508**, 340; e) H. H. Patel and M. S. Sigman, *J. Am. Chem. Soc.*, 2015, **137**, 3462; f) C. Zhang, C. B. Santiago, J. M. Crawford and M. S. Sigman, *J. Am. Chem. Soc.*, 2015, **137**, 15668; g) H. H. Patel and M. S. Sigman, *J. Am. Chem. Soc.*, 2016, **138**, 14226; h) F. Ozawa, A. Kubo and T. Hayashi, *J. Am. Chem. Soc.*, 1991, **113**, 1417; i) Z. Yang and J. Zhou, *J. Am. Chem. Soc.*, 2012, **134**, 11833; j) C. Wu and J. Zhou, *J. Am. Chem. Soc.*, 2014, **136**, 650; k) G. Yue, K. Lei, H. Hirao and J. Zhou, *Angew. Chem. Int. Ed.*, 2015, **54**, 6531; l) A. Faulkner and J. F. Bower, *Angew. Chem. Int. Ed.*, 2012, **51**, 1675; m) A. Faulkner, N. J. Race, J. S. Scott and J. F. Bower, *Chem. Sci.*, 2014, **5**, 2416; n) I. R. Hazelden, X. F. Ma, T. Langer and J. F. Bower, *Angew. Chem. Int. Ed.*, 2016, **55**, 11198.

[4]. S. Maity, R. Kancherla, U. Dhawa, E. Hoque, S. Pimparkar and D. Maiti, *ACS Catal.*, 2016, **6**, 5493.

[5]. a) L. Grigorjeva and O. Daugulis, *Org. Lett.*, 2014, **16**, 4684. For similar reactivity with alkyne, see: b) L. Grigorjeva and O. Daugulis, *Angew. Chem. Int. Ed.*, 2014, **53**, 10209. c) R. Mei, H. Wang, S. Warratz, S. A. Macgregor and L. Ackermann *Chem. Eur. J.*, 2016, **22**, 6759.

[6]. The Yu group had developed and utilized this directing scaffold in Pd and Cu-catalyzed reactions: a) R. Giri, N. Maugel, B. M. Foxman and J.-Q. Yu, *Organometallics*, 2008, **27**, 1667; b) M. Shang, S.-Z. Sun, H.-X. Dai and J.-Q. Yu, *Org. Lett.*, 2014, **16**, 5666; c) M. Shang, S.-Z. Sun, H.-X. Dai and J.-Q. Yu, *J. Am. Chem. Soc.*, 2014, **136**, 3354; d) M. Shang, S.-Z. Sun, H.-L. Wang, B. N. Laforteza, H.-X. Dai and J.-Q. Yu, *Angew. Chem. Int. Ed.*, 2014, **53**, 10439; e) M. Shang, H.-L. Wang, S.-Z. Sun, H.-X. Dai and J.-Q. Yu, *J. Am. Chem. Soc.*, 2014, **136**, 11590; f) S.-Z. Sun, M. Shang, H.-L. Wang, H.-X. Lin, H.-X. Dai and J.-Q. Yu, *J. Org. Chem.*, 2015, **80**, 8843.

[7]. a) R. F. Heck, *Acc. Chem. Res.*, 1979, **12**, 146; b) I. Moritani and Y. Fujiwara, *Tetrahedron Lett.*, 1967, **8**, 1119.

[8]. a) R. F. Heck, *J. Am. Chem. Soc.*, 1971, **93**, 6896; b) K. Kikukawa and T. Matsuda, *Chem. Lett.*, 1977, 159; c) K. Kikukawa, K. Nagira, F. Wada and T. Matsuda, *Tetrahedron*, 1981, **37**, 31; d) J. G. Taylor, A. V. Moro and C. R. D. Correia, *Eur. J. Org. Chem.*, **2011**, 1403; e) Y. Takahama, Y. Shibata and K. Tanaka, *Chem. Eur. J.*, 2015, **21**, 9053.

[9]. For previous instances of allylic selectivity with aliphatic olefins, see: a) D.-H. Wang, K. M. Engle, B.-F. Shi and J.-Q. Yu, *Science*, 2010, **327**, 315; b) K. M. Engle, D.-H. Wang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 14137; c) H. Li, Y. Li, X.-S. Zhang, K. Chen,

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X. Wang and Z.-J. Shi, *J. Am. Chem. Soc.*, 2011, **133**, 15244; d) B. Liu, Y. Fan, Y. Gao, C. Sun, C. Xu and J. Zhu, *J. Am. Chem. Soc.*, 2013, **135**, 468; e) Y. Takahama, Y. Shibata and K. Tanaka, *Org. Lett.*, 2016, **18**, 2934; f) R. Manoharan, G. Sivakumar and M. Jeganmohan, *Chem. Commun.*, 2016, **52**, 10533; g) T. Yamaguchi, Y. Kommagalla, Y. Aihara and N. Chatani, *Chem. Commun.*, 2016, **52**, 10129.

[10]. For allylation with activated olefins, see: a) D. Leow, G. Li, T.-S. Mei and J.-Q. Yu, *Nature*, 2012, **486**, 518; b) S. Bag, T. Patra, A. Modak, A. Deb, S. Maity, U. Dutta, A. Dey, R. Kancherla, A. Maji, A. Hazra, M. Bera and D. Maiti, *J. Am. Chem. Soc.*, 2015, **137**, 11888.

[11]. For selected references on important allylation chemistry, see: a) M. R. Luzung, C. A. Lewis and P. S. Baran, *Angew. Chem. Int. Ed.*, 2009, **48**, 7025; b) T. Yao, K. Hirano, T. Satoh and M. Miura, *Angew. Chem. Int. Ed.*, 2011, **50**, 2990; c) Y. Makida, H. Ohmiya and M. Sawamura, *Angew. Chem. Int. Ed.*, 2012, **51**, 4122; d) S. Asako, L. Ilies and E. Nakamura, *J. Am. Chem. Soc.*, 2013, **135**, 17755; e) H. Wang, N. Schroeder and F. Glorius, *Angew. Chem. Int. Ed.*, 2013, **52**, 5386; f) X. Cong, Y. Li, Y. Wei and X. Zeng, *Org. Lett.*, 2014, **16**, 3926; g) H. Jiang, W. Yang, H. Chen, J. Li and W. Wu, *Chem. Commun.*, 2014, **50**, 7202; h) T. Gensch, S. Vasquez-Cespedes, D.-G. Yu and F. Glorius, *Org. Lett.*, 2015, **17**, 3714; i) Y. Suzuki, B. Sun, K. Sakata, T. Yoshino, S. Matsunaga and M. Kanai, *Angew. Chem. Int. Ed.*, 2015, **54**, 9944; j) H.-P. Deng, D. Wang and K. J. Szabó, *J. Org. Chem.*, 2015, **80**, 3343; k) G. Cera, T. Haven and L. Ackermann, *Angew. Chem. Int. Ed.*, 2016, **55**, 1484; l) D. Zell, Q. Bu, M. Feldt and L. Ackermann, *Angew. Chem. Int. Ed.*, 2016, **55**, 7408; m) C. C. Pattillo, I. I. Strambeanu, P. Calleja, N. A. Vermeulen, T. Mizuno and M. C. White, *J. Am. Chem. Soc.*, 2016, **138**, 1265; n) H. Zhang, R.-B. Hu, N. Liu, S.-X. Li and S.-D. Yang, *Org. Lett.*, 2016, **18**, 28; o) S. E. Korkis, D. J. Burns and H. W. Lam, *J. Am. Chem. Soc.*, 2016, **138**, 12252; p) R. Y. Liu, Y. Yang and S. L. Buchwald, *Angew. Chem. Int. Ed.*, 2016, **55**, 14077; q) W. Liu, S. C. Richter, Y. Zhang and L. Ackermann, *Angew. Chem. Int. Ed.*, 2016, **55**, 7747; r) S. Y. Lee and J. F. Hartwig, *J. Am. Chem. Soc.*, 2016, **138**, 15278.

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