Communication

Ni-Catalyzed Regioselective Alkylarylation of Vinylarenes via C(sp3)-C(sp3)/C(sp3)-C(sp2) Bond Formation and Mechanistic Studies

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Ni-Catalyzed Regioselective Alkylarylation of Vinylarenes via C(sp³)-C(sp³)/C(sp³)-C(sp²) Bond Formation and Mechanistic Studies

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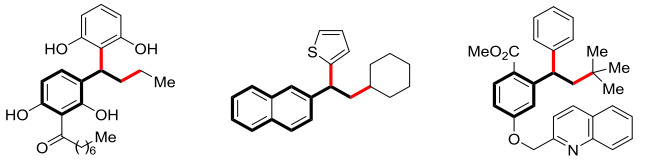
Supporting Information Placeholder

ABSTRACT: We report a Ni-catalyzed regioselective alkylarylation of vinylarenes with alkyl halides and arylzinc reagents to generate 1,1-diarylalkanes. The reaction proceeds well with primary, secondary and tertiary alkyl halides, and electronically diverse arylzinc reagents. Mechanistic investigations by radical probes, competition studies and quantitative kinetics reveal that the current reaction proceeds via a Ni(0)/Ni(I)/Ni(II) catalytic cycle by a rate-limiting direct halogen atom abstraction via single electron transfer (SET) to alkyl halides by a Ni(0) catalyst.

Regioselective difunctionalization of olefins by intercepting Heck C(sp³)-[M] intermediates with organometallic reagents[1] is a powerful method to construct complex molecules[2] rapidly from readily available starting materials.[3] However, the development of such a method is generally hindered by facile β-H elimination from the C(sp³)-[M] species leading to Heck products.[4] Recently, strategies to stabilize C(sp³)-[M] species in situ via π-allyl-[M] formation[5] and heteroatom coordination[6] have been successfully implemented to overcome the complications from β-H elimination,[7] which enabled their subsequent interception with organometallic reagents.[8] An alternative approach that proceeds by reductive coupling via radical intermediates[9] is also emerging as a powerful method for olefin dicarbofunctionalization.[10]

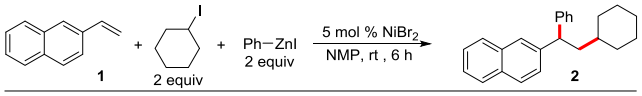
Vinylarenes serve as one of the most synthetically valuable sources of olefins, which could attenuate the effects of β-H elimination by in situ formation of π-benzyl-[M] species.[11] Dicarbofunctionalization of such olefins could afford a concise synthetic disconnection to construct 1,1-diarylalkanes, which show strong bioactivity against breast cancer (MCF-7), lung cancer (H-460), brain cancer (SF-268), and membrane protein FLAP (5-Lipoxygenase Acting Protein) (Scheme 1).[12] However, methods to dicarbofunctionalize vinylarenes are rare. The limited known examples of reactions proceed for homodicarboalkoxylation,[13] homodiarylation/homodivinylation,[11a] trifluoromethylarylation,[14] trifluoromethylcyanation[15] and vinylarylation.[11b] To the best of our knowledge, there is no general catalytic method for a three-component alkylarylation of vinylarenes to furnish 1,1-diarylalkanes.[16] Herein, we report a Ni-catalyzed alkylarylation of vinylarenes with primary, secondary and tertiary alkyl halides, and arylzinc reagents that furnishes diversely substituted 1,1-diarylalkanes via the formation of two C(sp³)-C(sp³) and C(sp³)-C(sp²) bonds in one step. Mechanistic studies indicate that the reaction proceeds by a rate-limiting direct halogen atom abstraction via single electron transfer (SET) from a Ni(0) catalyst to alkyl halides.



Scheme 1. Bioactive 1,1-diarylalkanes

We began our studies by attempting to alkylarylate 2-vinylnaphthalene with cyclohexyl iodide and PhZnI with different transition metal catalysts (Table 1). We were pleased to find that the reaction was efficiently catalyzed by 5 mol% $NiBr_2$ in NMP at room temperature affording the alkylarylated product **2** in 81% yield with 2 equiv each of cyclohexyl iodide and PhZnI (entry 1).[17] Lowering the amount of cyclohexyl iodide or PhZnI decreased the yield (entries 2-3). Alkyl fluoride did not form any product (entry 4).[16c] The reaction is also catalyzed by $Ni(cod)_2$ and $(Ph_3P)_4Ni$ in similar yields (entries 5-6). While $CoCl_2$ also catalyzed the reaction in moderate yields (entry 7), Fe, Cu and Pd-catalysts did not form any product (entry 8). The reaction also did not proceed in the absence of $NiBr_2$ (entry 9). While the reaction proceeded in a similar yield in DMA, only a small amount of the product **2** was formed in THF or toluene (entries 10-11).

Table 1. Optimization of reaction conditions[a]



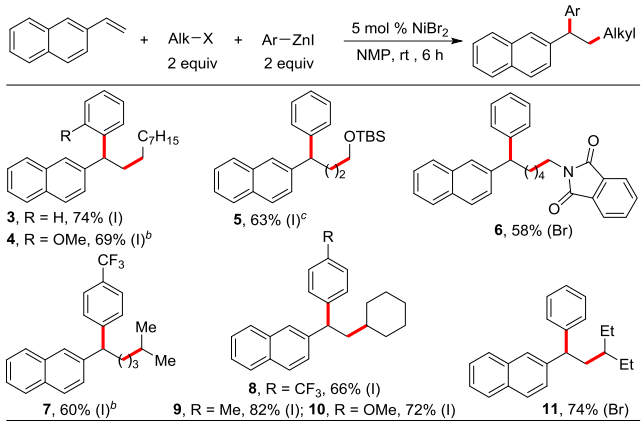
entry	modified conditions	yield of **2** (%)
1	none	87 (81)[b]
2	1.5 equiv cyclohexyl iodide	59
3	1.5 equiv of PhZnI	69
4	1-fluorodecane instead of cyclohexyl iodide	0
5	$Ni(cod)_2$ instead of $NiBr_2$	87
6	$(Ph_3P)_4Ni$ instead of $NiBr_2$	68
7	$CoCl_2$ instead of $NiBr_2$	40
8	$Pd(OAc)_2$, $FeCl_2$ or CuI instead of $NiBr_2$	0
9	without $NiBr_2$	0
10	DMA instead of NMP	70
11	THF or toluene instead of NMP	5-9

[a]0.1 mmol scale reactions. [b]Isolated yield (0.5 mmol scale) in parenthesis.

With the optimized conditions, we examined the scope of the alkylarylation of 2-vinylnaphthalene with a variety of alkyl halides and arylzinc reagents (Table 2).[18] The reaction proceeds well with primary and secondary alkyl halides (I, Br), and generates products

with secondary and tertiary carbon centers. The reaction also tolerates various functional groups such as OTBS (**5**), phthalimide (**6**), CF_3 (**7**-**8**) and OMe (**4**, **10**), and ArZnI bearing *ortho*-OMe (**4**).

Table 2. Scope with RX and ArZnI[a]



[a]0.5 mmol scale reactions. Letters in parenthesis indicate X in Alkyl-X. [b]5 mol% $Ni(cod)_2$. [c]8 h.

The current alkylarylation reaction can be conducted with a wide range of vinylarenes (Table 3).[18] The reaction can be performed with vinylarenes containing various functional groups such as Cl (**15**-**17**, **21**, **22**), Ph (**18**), OMe (**19**, **32**), esters (**20**, **25**) and ketones (**30**). Alkyl halides containing functional groups such as Cl (**12**), OEt (**13**), OTBS (**16**), olefins (**17**) and NCbz (**24**) can be used as coupling partners. ArZnI containing sensitive functional groups like esters (**22**) and CN (**29**) are tolerated. The reaction also proceeds with vinyl bromides (**25**).

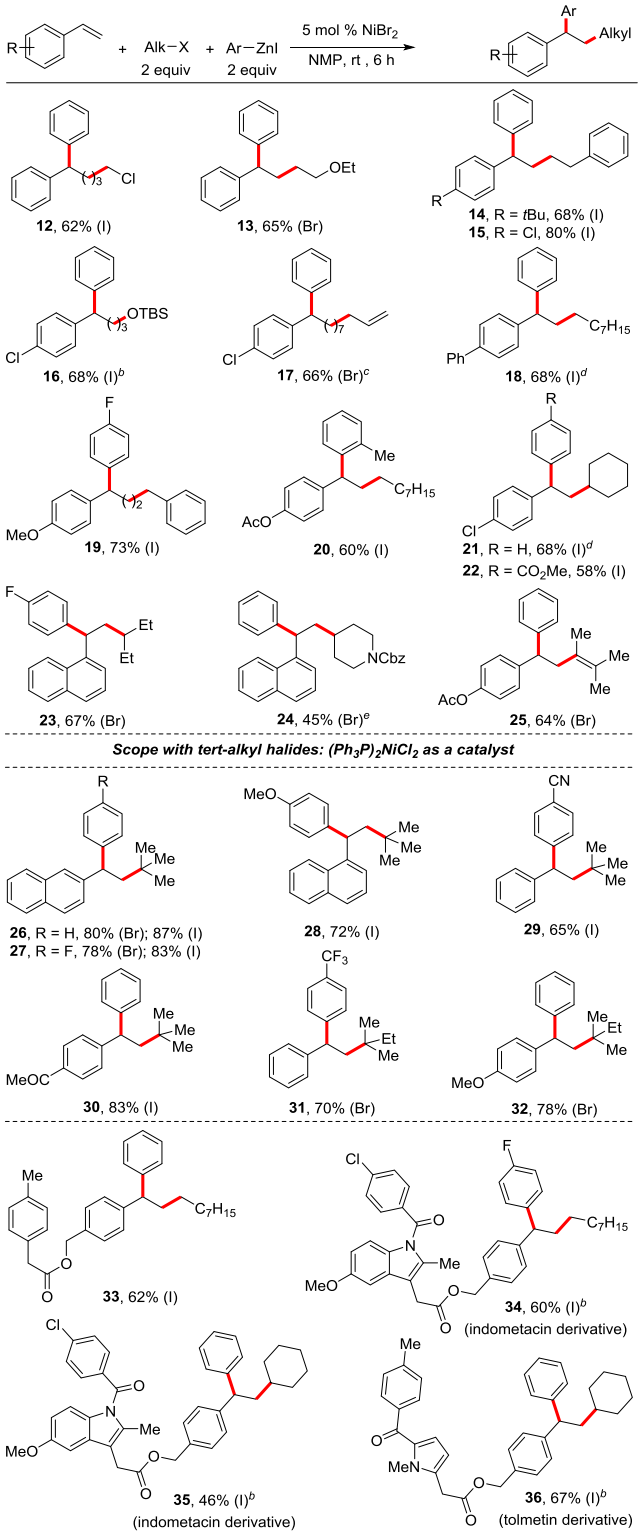
The reactions of *tert*-alkyl halides proved more challenging than those of the primary and secondary alkyl halides. The reaction with tertiary alkyl halides typically produced products in low yields except for the coupling of *tert*-BuBr and PhZnI with 2-vinylnaphthalene (**26**). Further catalyst optimization showed that $(Ph_3P)_2NiCl_2$ was an excellent catalyst for the coupling with *tert*-alkyl halides, which afforded products with quaternary carbon centers in good to excellent yields (**26**-**32**).

We have also demonstrated the synthetic utility of the alkylarylation reaction in modified drug derivatives (**34**-**36**). Vinylarenes built on the backbones of two non-steroidal anti-inflammatory drugs (NSAIDs), indometacin and tolmetin, were alkylarylated efficiently with ArZnI and primary and secondary alkyl halides, which afforded the corresponding products **34**-**36** in 46-67% yields.

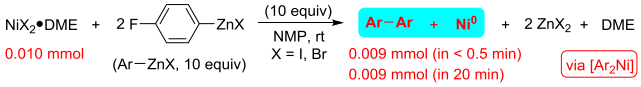
We also conducted mechanistic studies to understand the process of alkylarylation. Since the current reaction is also catalyzed by $Ni(cod)_2$ and $(Ph_3P)_4Ni$ similar to $NiBr_2$ (Table 1), we believe that Ni(0) is the active catalyst wherein $NiBr_2$ is reduced by ArZnI to Ni(0). In order to examine this possibility, we performed a reaction of $NiBr_2$•DME with access of 4-FC_6H_5ZnI in the presence of 2-vinylnaphthalene and analyzed the dark solution formed instantaneously upon mixing by ^{19}F NMR. The reaction furnished 4,4'-difluorobiphenyl in a near stoichiometric molar ratio to that of $NiBr_2$•DME immediately and the concentration of the biaryl remained constant over time (Scheme 2). This experiment indicates that $NiBr_2$ is instantaneously reduced to Ni(0) in the presence of ArZnI reagents under our reaction conditions via fast double transmetalation with ArZnI and reductive elimination of biaryls.

We then conducted a radical clock experiment using iodoethoxypropene as a radical probe (Scheme 3).[10m] When iodoethoxypropene was reacted with 4-chlorostyrene and PhZnI under the standard reaction condition, cyclized product **37** was generated in 38% yield. In addition, we also isolated the dimer **38** along with the

Table 3. Scope with vinylarenes, RX and ArZnI[a]

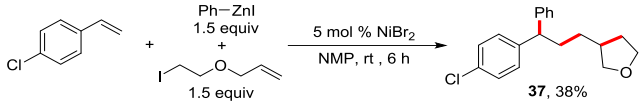


[a]0.5 mmol scale reactions. Letters in parenthesis indicate X in Alkyl-X. [b]8 h. [c]10 mol% $NiBr_2$. [d]5 mol% $Ni(cod)_2$. [e]50 °C, 12 h.

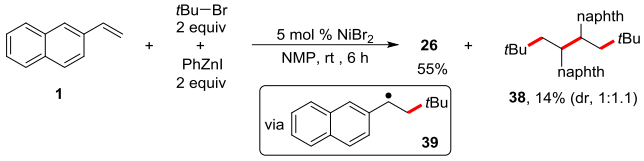


Scheme 2. Reduction of Ni(II) to Ni(0) by ArZnI

expected product **26** in 14% and 55% yields, respectively, when olefin **1** was reacted with *t*BuBr and PhZnI (Scheme 4). The product **38** arises from dimerization of the benzylic radical **39**. These results indicate that the alkylarylation of vinylarenes proceeds by a single electron transfer (SET) process.



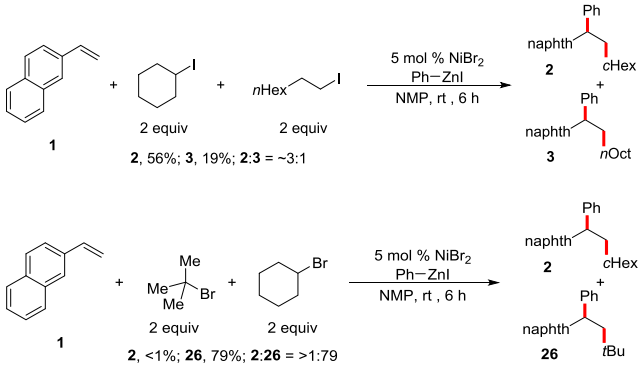
Scheme 3. Radical clock experiment



Scheme 4. Formation of radically dimerized product

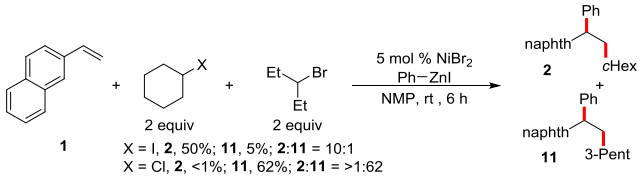
We also performed competition experiments with different alkyl halides. Competitions between *n*-octyl iodide and cyclohexyl iodide, and between cyclohexyl bromide and *t*-butyl bromide showed that *t*-alkyl halides reacted faster than *s*-alkyl halides, and *s*-alkyl halides reacted faster than *n*-alkyl halides (*t*-RX > *s*-RX > *n*-RX) (Scheme 5). Similar competition between *s*-alkyl iodide and *s*-alkyl bromide, and *s*-alkyl bromide and *s*-alkyl chloride indicated that alkyl iodides reacted faster than alkyl bromides, and alkyl bromides reacted faster than alkyl chlorides (RI > RBr > RCl) (Scheme 6). These results are consistent with the reaction proceeding by a rate-limiting direct halogen atom abstraction from alkyl halides via inner sphere electron transfer from a Ni-catalyst.[19]

We also performed a competition between 4-$CF_3C_6H_4$ZnI and 4-$MeOC_6H_4$ZnI, which produced the corresponding alkylarylated products **8** and **10** in nearly a 1:1 ratio (Scheme 7). This result indicated that the reaction experienced no rate difference towards electronically biased ArZnI and that ArZnI reagents were less likely involved in the rate-determining step (RDS).

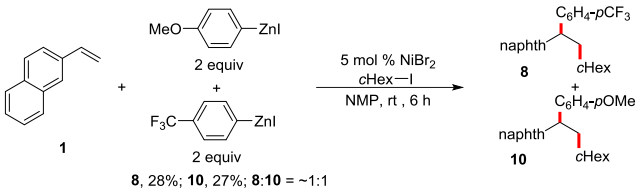


Scheme 5. Competition experiments with 1°, 2° and 3° R-X

We finally conducted quantitative kinetic studies in order to determine the roles of ArZnI, alkyl halides and vinylarenes at the RDS. Measurements of the initial rates (k_{in}) for the reaction of 2-vinylnaphthalene and PhZnI with different concentrations of cyclohexyl iodide and the catalyst showed a corresponding rise in the



Scheme 6. Competition experiments with RI, RBr and RCl



Scheme 7. Competition experiments with ArZnI

rates of the reactions. Plots of k_{in} versus the concentrations of cyclohexyl iodide and the catalyst gave linear curves (slope = 1.61 × 10^{-4} M s^{-1}; 7.3 × 10^{-3} M s^{-1}) indicating a first order rate dependence on RX and the catalyst (Fig. 1a-b). Similar kinetic studies by varying the concentration of PhZnI, however, showed no change in k_{in} (Fig. 1c) suggesting that the reaction is zero order on ArZnI. Measurements of reaction progress with increasing concentrations of 2-vinylnaphthalene showed that the reaction rates were slightly affected negatively (Fig. 1d). These qualitative and quantitative kinetic studies suggest that the reaction with alkyl halides by direct halogen atom abstraction is rate-limiting, and that the increased concentration of 2-vinylnaphthalene interferes with the reaction rate by multiple ligation to the Ni(0)-catalyst, which depletes coordination sites for complexing alkyl halides at the transition state required for inner sphere electron transfer during direct halogen atom abstraction.[19]

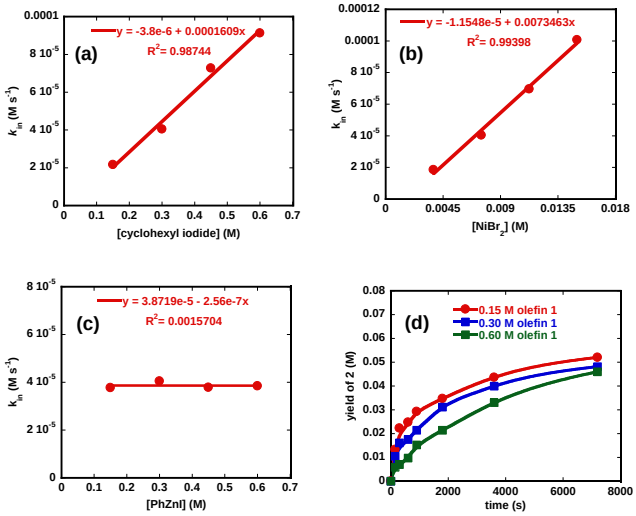
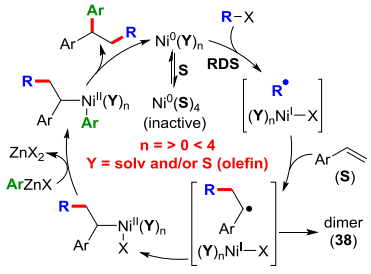


Figure 1. (a) A plot of k_{in} vs. cyclohexyl iodide concentrations. (b) A plot of k_{in} vs. $NiBr_2$ concentrations. (c) A plot of k_{in} vs. PhZnI concentrations. (d) A plot of product yields vs. olefin **1** concentrations.



Scheme 8: Proposed catalytic cycle

Based on these mechanistic studies, we propose a catalytic cycle (Scheme 8). Herein, the reaction is initiated by a solvent/olefin-stabilized Ni(0)-catalyst, which reduces alkyl halides by SET and generates alkyl radicals (R•) by a rate-limiting halogen atom abstraction process. The alkyl radicals then undergo addition to olefins to

form benzylic radicals. The subsequent steps of recombination of the benzylic radicals with the [Ni^{I}-X] species followed by transmetalation with ArZnX and reductive elimination produce the alkylarylated products and regenerate the active Ni(0)-catalyst.

In summary, we have developed a Ni-catalyzed regioselective alkylarylation of vinylarenes to generate 1,1-diarylalkanes via the formation of two C(sp^3)-C(sp^3) and C(sp^3)-C(sp^2) bonds in one step. The reaction works well with primary, secondary and tertiary alkyl halides, and a variety of arylzinc reagents. Mechanistic studies by radical probes, competition experiments and quantitative kinetics indicate that the reaction proceeds by a rate-limiting halogen atom abstraction via SET from a Ni(0) catalyst to alkyl halides.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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REFERENCES

(1) For reviews, see: (a) Derosa, J. T., V. T.; van der Puyl; V. A.; Engle, K. M. *Aldrichimica Acta* **2018**, *51*, 21; (b) Giri, R.; Kc, S. *J. Org. Chem.* **2018**, *83*, 3013; (c) Dhungana, R. K.; KC, S.; Basnet, P.; Giri, R. *Chem. Rec.* **2018**, doi:10.1002/tcr.201700098.

(2) For examples of difunctionalization of activated olefins, see: (a) Qin, T.; Cornella, J.; Li, C.; Malins, L. R.; Edwards, J. T.; Kawamura, S.; Maxwell, B. D.; Eastgate, M. D.; Baran, P. S. *Science* **2016**, *352*, 801; (b) Zhang, L.; Lovinger, G. J.; Edelstein, E. K.; Szymaniak, A. A.; Chierchia, M. P.; Morken, J. P. *Science* **2016**, *351*, 70.

(3) For reviews on olefin difunctionalization to form C-C/C-O,N bonds, see: (a) Chemler, S. R.; Karyakarte, S. D.; Khoder, Z. M. *J. Org. Chem.* **2017**, *82*, 11311; (b) Gockel, S. N.; Buchanan, T. L.; Hull, K. L. *J. Am. Chem. Soc.* **2018**, *140*, 58; (c) Wolfe, J. P. *Synlett* **2008**, *2008*, 2913.

(4) For Ni-catalyzed Heck reactions, see: (a) Matsubara, R.; Gutierrez, A. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2011**, *133*, 19020; (b) Harris, M. R.; Konev, M. O.; Jarvo, E. R. *J. Am. Chem. Soc.* **2014**, *136*, 7825; (c) Gøgsig, T. M.; Kleimark, J.; Nilsson Lill, S. O.; Korsager, S.; Lindhardt, A. T.; Norrby, P.-O.; Skrydstrup, T. *J. Am. Chem. Soc.* **2012**, *134*, 443; (d) Desrosiers, J.-N.; Hie, L.; Biswas, S.; Zatolochnaya, O. V.; Rodriguez, S.; Lee, H.; Grinberg, N.; Haddad, N.; Yee, N. K.; Garg, N. K.; Senanayake, C. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 11921; (e) Maity, S.; Dolui, P.; Kancherla, R.; Maiti, D. *Chem. Sci.* **2017**, *8*, 5181; (f) Huihui, K. M. M.; Shrestha, R.; Weix, D. J. *Org. Lett.* **2017**, *19*, 340.

(5) (a) Mizutani, K.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2003**, *5*, 3959; (b) Liao, L.; Jana, R.; Urkalan, K. B.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 5784; (c) McCammant, M. S.; Liao, L.; Sigman, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 4167; (d) Wu, X.; Lin, H.-C.; Li, M.-L.; Li, L.-L.; Han, Z.-Y.; Gong, L.-Z. *J. Am. Chem. Soc.* **2015**, *137*, 13476; (e) Iwasaki, T.; Fukuoka, A.; Yokoyama, W.; Min, X.; Hisaki, I.; Yang, T.; Ehara, M.; Kuniyasu, H.; Kambe, N. *Chem. Sci.* **2018**, *9*, 2195; (f) Jun, T.; Shinsuke, N.; A., C. F.; Akifumi, N.; Nobuaki, K. *Adv. Synth. Catal.* **2004**, *346*, 905.

(6) (a) Trejos, A.; Fardost, A.; Yahiaoui, S.; Larhed, M. *Chem. Commun.* **2009**, 7587; (b) Gu, J.-W.; Min, Q.-Q.; Yu, L.-C.; Zhang, X. *Angew. Chem. Int. Ed.* **2016**, *55*, 12270; (c) Shrestha, B.; Basnet, P.; Dhungana, R. K.; Kc, S.; Thapa, S.; Sears, J. M.; Giri, R. *J. Am. Chem. Soc.* **2017**, *139*, 10653; (d) Derosa, J.; Tran, V. T.; Boulous, M. N.; Chen, J. S.; Engle, K. M. *J. Am. Chem. Soc.* **2017**, *139*, 10657; (e) Thapa, S.; Dhungana, R. K.; Magar, R. T.; Shrestha, B.; Kc, S.; Giri, R. *Chem. Sci.* **2018**, *9*, 904; (f) Derosa, J.; van der Puyl, V. A.; Tran, V. T.; Liu, M.; Engle, K. M. *Chem. Sci.* **2018**, *9*, 5278; (g) Li, W.; Boon, J. K.; Zhao, Y. *Chem. Sci.* **2018**, *9*, 600.

(7) For olefin 1,1-difunctionalization by β-H elimination/Pd-H re-insertion steps, see: (a) Orlandi, M.; Hilton, M. J.; Yamamoto, E.; Toste, F. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2017**, *139*, 12688; (b) Saini, V.; Sigman, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 11372; (c) Werner, E. W.; Urkalan, K. B.; Sigman, M. S. *Org. Lett.* **2010**, *12*, 2848.

(8) For olefin dicarbofunctionalization via carbometallation, see: Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978.

(9) (a) García-Domínguez, A.; Li, Z.; Nevado, C. *J. Am. Chem. Soc.* **2017**, *139*, 6835; (b) Terao, J.; Saito, K.; Nii, S.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1998**, *120*, 11822.

(10) For selected examples of olefin dicarbofunctionalization by cyclization, see: (a) Stadtmueller, H.; Lentz, R.; Tucker, C. E.; Stuedemann, T.; Doerner, W.; Knochel, P. *J. Am. Chem. Soc.* **1993**, *115*, 7027; (b) Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 5374; (c) Phapale, V. B.; Buñuel, E.; García-Iglesias, M.; Cárdenas, D. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 8790; (d) Cong, H.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 3788; (e) You, W.; Brown, M. K. *J. Am. Chem. Soc.* **2014**, *136*, 14730; (f) You, W.; Brown, M. K. *J. Am. Chem. Soc.* **2015**, *137*, 14578; (g) McMahon, C. M.; Renn, M. S.; Alexanian, E. J. *Org. Lett.* **2016**, *18*, 4148; (h) Dhungana, R. K.; Shrestha, B.; Thapa-Magar, R.; Basnet, P.; Giri, R. *Org. Lett.* **2017**, *19*, 2154; (i) Thapa, S.; Basnet, P.; Giri, R. *J. Am. Chem. Soc.* **2017**, *139*, 5700; (j) Xu, T.; Dong, G. *Angew. Chem. Int. Ed.* **2012**, *51*, 7567; (k) Walker, J. A.; Vickerman, K. L.; Humke, J. N.; Stanley, L. M. *J. Am. Chem. Soc.* **2017**, *139*, 10228; (l) Xiao, J.; Cong, X.-W.; Yang, G.-Z.; Wang, Y.-W.; Peng, Y. *Chem. Commun.* **2018**, *54*, 2040; (m) Kc, S.; Basnet, P.; Thapa, S.; Shrestha, B.; Giri, R. *J. Org. Chem.* **2018**, *83*, 2920; (n) Nakamura, M.; Ito, S.; Matsuo, K.; Nakamura, E. *Synlett* **2005**, *2005*, 1794.

(11) (a) Urkalan, K. B.; Sigman, M. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 3146; (b) Kuang, Z.; Yang, K.; Song, Q. *Org. Lett.* **2017**, *19*, 2702; (c) Jun, T.; Yuichiro, K.; Nobuaki, K. *Chem. Asian J.* **2008**, *3*, 1472.

(12) (a) Sanchez, L. A.; Olmedo, D.; Lopez-Perez, J. L.; Williams, T. D.; Gupta, M. P. *Nat. Prod. Commun.* **2012**, *7*, 1043; (b) Chu, L.; Armstrong, H. M.; Chang, L. L.; Cheng, A. F.; Colwell, L.; Cui, J.; Evans, J.; Galka, A.; Goulet, M. T.; Hayes, N.; Lo, J.; Menke, J.; Ok, H. O.; Ondeyka, D. L.; Patel, M.; Quaker, G. M.; Sings, H.; Witkin, S. L.; Zhao, A.; Ujjainwalla, F. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4133; (c) Yonova, I. M.; Johnson, A. G.; Osborne, C. A.; Moore, C. E.; Morrissette, N. S.; Jarvo, E. R. *Angew. Chem. Int. Ed.* **2014**, *53*, 2422.

(13) (a) Heck, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 2712; (b) James, D. E.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 1810.

(14) (a) Wang, F.; Wang, D.; Mu, X.; Chen, P.; Liu, G. *J. Am. Chem. Soc.* **2014**, *136*, 10202; (b) Wu, L.; Wang, F.; Wan, X.; Wang, D.; Chen, P.; Liu, G. *J. Am. Chem. Soc.* **2017**, *139*, 2904.

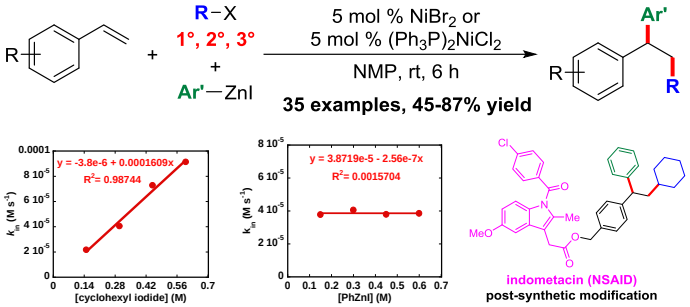
(15) (a) Ilchenko, N. O.; Janson, P. G.; Szabó, K. J. *J. Org. Chem.* **2013**, *78*, 11087; (b) He, Y.-T.; Li, L.-H.; Yang, Y.-F.; Zhou, Z.-Z.; Hua, H.-L.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2014**, *16*, 270; (c) Wang, F.; Wang, D.; Wan, X.; Wu, L.; Chen, P.; Liu, G. *J. Am. Chem. Soc.* **2016**, *138*, 15547.

(16) (a) For a stoichiometric Ag-mediated α-alkyl-indolation of styrenes, see: Ouyang, X.-H.; Song, R.-J.; Hu, M.; Yang, Y.; Li, J.-H. *Angew. Chem. Int. Ed.* **2016**, *55*, 3187; (b) For a visible light/Ir-catalyzed α-alkyl-indolation of styrenes, see: Li, M.; Yang, J.; Ouyang, X.-H.; Yang, Y.; Hu, M.; Song, R.-J.; Li, J.-H. *J. Org. Chem.* **2016**, *81*, 7148; (c) For alkylarylation of dienes, see: Takanori, I.; Xin, M.; Asuka, F.; Hitoshi, K.; Nobuaki, K. *Angew. Chem. Int. Ed.* **2016**, *55*, 5550..

(17) For selected examples of Ni-catalyzed Negishi coupling, see: (a) Schmidt, J.; Choi, J.; Liu, A. T.; Slusarczyk, M.; Fu, G. C. *Science* **2016**, *354*, 1265; (b) Schley, N. D.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 16588; (c) Liang, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 5520; (d) Joshi-Pangu, A.; Ganesh, M.; Biscoe, M. R. *Org. Lett.* **2011**, *13*, 1218.

(18) The mass balance is accounted for by the remaining vinylarenes and 5-10% of the alkyl Heck and hydroarylated products.

(19) Huber, T. A.; Macartney, D. H.; Baird, M. C. *Organometallics* **1995**, *14*, 592.


R
+
R−X
1°, 2°, 3°
+
Ar'—ZnI
5 mol % NiBr2 or
5 mol % (Ph3P)2NiCl2
NMP, rt, 6 h
35 examples, 45-87% yield
Ar'
R
y = -3.8e-6 + 0.0001609x
R2= 0.98744
[cyclohexyl iodide] (M)
y = 3.8719e-5 - 2.56e-7x
R2= 0.0015704
[PhZnI] (M)
Cl
MeO
Me
indometacin (NSAID)
post-synthetic modification