Title: Integrating Allyl Electrophiles into Nickel-Catalyzed Conjunctive Cross-Coupling

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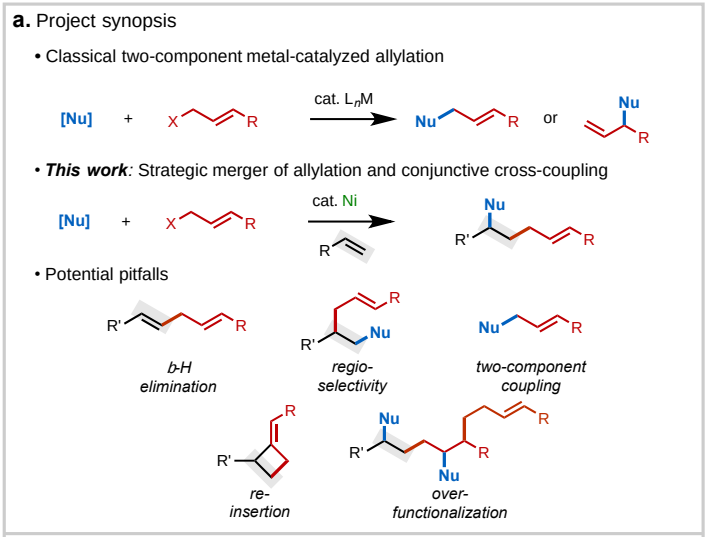
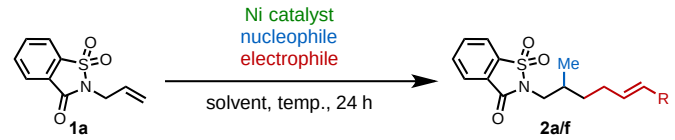
Abstract: Allylation and conjunctive cross-coupling represent two useful, yet largely distinct, reactivity paradigms in catalysis. The union of these two processes would offer exciting possibilities in organic synthesis but remains largely unknown. Herein, we report the use of allyl electrophiles in nickel-catalyzed conjunctive cross-coupling with a non-conjugated alkene and dimethylzinc. The transformation is enabled by weakly coordinating, monodentate azaheterocycle directing groups, that useful building blocks in synthesis, including saccharin, pyridones, pyrazoles, and triazoles. The reaction occurs under mild conditions and is compatible with a wide range of allyl electrophiles. High chemoselectivity through substrate directivity is demonstrated in the facile reactivity of the β-γ alkene of the starting material, while the ε-ζ alkene of the product is preserved. The generality of this approach is further illustrated through the development of analogous method with alkyne substrates. Mechanistic studies reveal the importance of the weakly coordinating directing group in dissociating to allow binding of the allyl moiety to facilitate $C(sp^3)$–$C(sp^3)$ reductive elimination.



b. Optimization of model reaction[a]



Entry	Electrophile (2 equiv)	Nucleophile	Ni cat.	Solvent (Temp)	2a/f [%][b]	1a [%][b]
1	allyl bromide	3 equiv $ZnMe_2$	20% $Ni(cod)_2$	dioxane (80 °C)	29	0
2	allyl chloride	3 equiv $ZnMe_2$	20% $Ni(cod)_2$	dioxane (80 °C)	45	0
3	allyl acetate	3 equiv $ZnMe_2$	20% $Ni(cod)_2$	dioxane (80 °C)	47	0
4	allyl acetate	3 equiv $ZnMe_2$	20% $Ni(cod)_2$	dioxane (rt)	52	0
5	allyl acetate	2 equiv $ZnMe_2$	20% $Ni(cod)_2$	dioxane (rt)	52	0
6	allyl acetate	2 equiv MeMgI	20% $Ni(cod)_2$	dioxane (rt)	25	63
7	allyl acetate	2 equiv $ZnMe_2$	20% $Ni(cod)_2$	dioxane 0 °C	56	0
8	allyl acetate	2 equiv $ZnMe_2$	20% $Ni(cod)_2$	2-MeTHF (–40 to 0 °C)	70	10
9	cinnamyl acetate	2 equiv $ZnMe_2$	20% $Ni(cod)_2$	2-MeTHF (–40 to 0 °C)	93	0
10	cinnamyl acetate	2 equiv $ZnMe_2$	10% $Ni(cod)_2$	2-MeTHF (–40 to 0 °C)	87	0
11	cinnamyl acetate	2 equiv $ZnMe_2$	10% $NiCl_2$	2-MeTHF (–40 to 0 °C)	5	87
12	cinnamyl acetate	2 equiv $ZnMe_2$	10% $NiCl_2$(glyme)	2-MeTHF (–40 to 0 °C)	81	0
13	cinnamyl acetate	2 equiv $ZnMe_2$	10% $NiBr_2$(glyme)	2-MeTHF (–40 to 0 °C)	99	0

Figure 1. a, Overview of prior art and conceptual blueprint. **b**, Optimization of reaction conditions. [a] Reaction conditions: **1a** (0.1 mmol), electrophile (0.3 or 0.2 mmol), solvent (0.3 mL). [b] Yields determined by ^{1}H NMR analysis using CH_2Br_2 as internal standard.

Main Text: The catalytic coupling of allyl electrophiles with various nucleophiles via the intermediacy of a π-allylmetal species is a powerful mode of bond construction in organic synthesis (Figure 1a, top).[1–5] The utility of this type of reaction stems from its ability to forge new C(sp^3)–C and C(sp^3)–heteroatom bonds, while simultaneously introducing an alkenyl moiety that can participate in diverse downstream alkene functionalization chemistry and is a useful motif in its own right. Two-component allylations, including the Tsuji–Trost reaction[1–5] and cross-coupling with organometallic nucleophiles,[6–19] are well-established and viewed as essential components of the modern synthetic repertoire.

Given the empowering nature of catalytic allylations, developing a toolkit of generally useful three-component allylations using alkenes as conjunctive reagents would enable rapid access to complex structures from simple starting materials. Recently, conjunctive cross-coupling (1,2-dicarbofunctionalization) with nickel and other metal catalysts has emerged as a valuable approach for conjoining organometallic nucleophiles, organohalide electrophiles, and alkenes.[20–21] Reactivity and selectivity in these reactions can be controlled through use of conjugated substrates (e.g., styrenes, acrylates, or related activated alkenes), which react to form a stabilized allyl–metal intermediate or a metal enolate intermediate.[22–25] As a complementary strategy our lab[26–28] and others[23,24,29–33] have developed analogous transformations with non-

conjugated substrates containing proximal coordinating groups, which react via metallacycle intermediates. While alkyl, aryl, alkenyl, and alkynyl halide electrophiles have been extensively studied in conjunctive cross-coupling with alkenes,[20–33] use of allyl electrophiles remains rare. Notably, Semba and Nakao have described a palladium/copper dual catalytic system for carboallylation of conjugated, electron-deficient alkenes; however, the reaction required doubly activated substrates, such as benzalmalononitrile, thereby limiting the types of product structures that can be accessed.[34–35] The goal of the present study was to develop a nickel-catalyzed conjunctive cross-coupling with allyl electrophiles and unactivated alkenes, thereby combining the benefits of these two distinct catalytic couplings (Figure 1a, middle).

At the outset we anticipated several fundamental challenges that would need to be overcome in the proposed system (Figure 1a, bottom). For instance, in alkene 1,2-difunctionalizations in general, the alkylmetal species that is formed upon migratory insertion is prone to subsequent rapid β-hydride elimination, generating the undesired Heck product. In this case, the proposed cycle would involve a C(sp^3)–C reductive elimination step, which may be kinetically inaccessible, causing β-hydride elimination to be favored. With non-conjugated alkene substrates, there are further challenges in the form of diminished reactivity and low chemo- and regioselectivity. With a less reactive alkene, undesired two-component allylation could predominate. Furthermore, when attempting to install an allyl group, the allyl coupling partner and/or resulting alkene product might be prone to additional insertion events under the reaction conditions, leading to product degradation and oligomerization. Indeed, early studies from the 1970s on nickel-mediated 1,2-allylfunctionalization of alkenes were limited to carbonylation reactions or resulted in undesired rearrangements leading to mixtures of products.[36–39]

With these considerations in mind and based on our lab's experience in developing substrate-directed nickel-catalyzed 1,2-difunctionalization reactions,[26–28,40] we sought to develop a three-component 1,2-allylalkylation reaction. Given that alkene ligands have been previously found to promote challenging C(sp^3)–C reductive eliminations (as required in our design),[28,41–47] we reasoned that the reaction could be facilitated by a weakly coordinating, monodentate directing group capable of dissociating to allow the allyl group to serve as an alkene ligand. We were further motivated to establish conditions that would enable a diverse range of useful aza-heterocycles to function as weak directing groups, thereby maximizing the synthetic flexibility of the method.

Indeed, in a series of preliminary experiments, we found that use of *N*-allyl saccharin in presence of an allyl electrophile and $ZnMe_2$ as nucleophile allowed simultaneous methylation at the β-position and allylation at the γ-position while preserving the resulting ε-alkene in the product (Figure 1b). We were pleased to observe that $ZnMe_2$ was a competent nucleophilic component, despite requiring a notoriously difficult $C(sp^3)$–$C(sp^3)$ reductive elimination step. Interestingly, while several other monodentate heterocycles were competent directing groups (*vide infra*), when we attempted the reaction on a bidentate 8-aminoquinoline-tethered 3-butenamide substrate that had been commonly used in previous difunctionalization reactions,[26,27,40] we observed no reaction and decomposition of starting material. Other related directing groups such as sulfinamide, acetamide, and carboxylic acid were also tested but were unsuccessful (See Supplementary Information).

After identifying saccharin as the lead directing group and acetate as the best leaving group, we sought to ameliorate the issue of starting material decomposition, which we surmised occurred via oxidative addition of low-valent nickel to the starting material. Although we screened a variety of ligands, none showed improvement in yield, and only a handful allowed some preservation of starting material (See Supplementary Information). Fortunately, we found that by lowering the temperature of the reaction and replacing the allyl acetate electrophile with an allyl cinnamate electrophile, we were able to significantly improve the yield without needing an external ligand. A quick examination of various nickel precatalysts showed that the reaction performed well with the bench-stable and inexpensive precatalyst $NiBr_2$(glyme), thereby concluding optimization.

We then explored a variety of different allyl and cinnamyl electrophiles (Figure 2). Various substituents were well-tolerated at the 1-, 2-, and 3-positions (**2b–e**). With cinnamyl electrophiles, electron-neutral (**2f–j**), electron-donating (**2k–o**), and electron-withdrawing (**2p–r, 2t–w**) substituents all resulted in good to excellent yields. Sensitive functional groups, such as esters and ketones, could be incorporated with high yields (**2p–q**). Thiophene (**2r**) and furan (**2s**) heterocycles could also be incorporated with moderate to good yields. Furthermore, chloro (**2v**) and bromo (**2w**) substituents were well-tolerated, opening possibilities for downstream modification through orthogonal cross-coupling chemistry.

We found that an α-branched substrate was compatible and offered high diastereoselectivity, albeit with attenuated reactivity (**2x–y**). Internal alkenes and 1,1-disubstituted alkenes showed no reaction under optimal

conditions. Among several alkyl- and arylzinc reagents that were examined, dimethylzinc proved to be uniquely effective. This observation is consistent with previously documented trends in transition-metal-catalyzed cross-coupling, where methyl coupling partners have been shown to have distinct reactivity.[48–50] In our system, we believe that this reactivity pattern reflects the sterically encumbered nature of the nickelacycle intermediate (vide infra). Nevertheless, the ability to facilitate $C(sp^3)$–$C(sp^3)$ reductive elimination using only a weakly coordinating directing group[26,27] and no additional ancillary ligand[51] is notable and suggestive of alkene involvement in this step.

Next, we examined whether this mode of reactivity could be extended to alkyne difunctionalization and found *N*-homopropargyl saccharin substrates to be compatible under similar reaction conditions to give skipped diene products. The corresponding propargylic saccharin substrates resulted in decomposition of starting material and no observable formation of the desired allylmethylation product. Both terminal (**3a**) and internal (**3b**) alkynes could be tolerated to give methylation at the γ-position and allylation at the δ-position. With an internal, phenyl-substituted substrate (**3c**), we observed methylation at the δ-position and allylation at the γ-position, which may be due to the steric encumbrance of the aryl ring and/or preferential formation of the stabilized styrenylnickel intermediate. These skipped dienes may serve as amine analogues to natural polyunsaturated fatty acids.

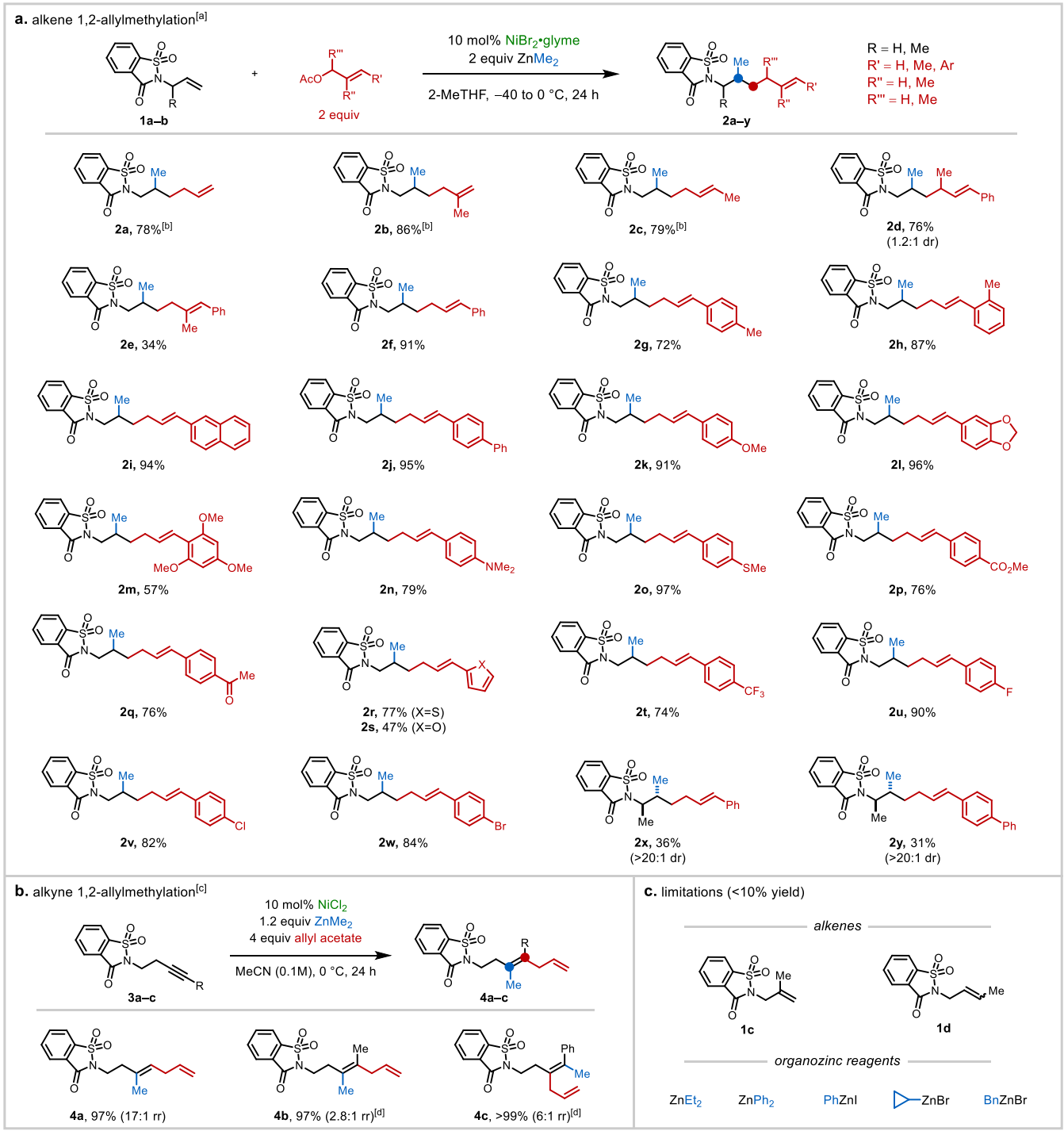


Figure 2. Scope of 1,2-allylmethylation method. **a**, Results with different allyl electrophiles and alkene substrates. [a] Reaction conditions: **1a–b** (0.2 mmol), $NiBr_2$•glyme (0.02 mmol), allyl electrophile (0.4 mmol), $ZnMe_2$ (0.4 mmol), 2-Me-THF (0.6 mL). Percentages represent isolated yields. [b] $Ni(cod)_2$ (0.04 mmol) as catalyst. **b**, Extension to alkyne substrates. [c] Reaction conditions: **3a** (0.2 mmol), $NiCl_2$ (0.02 mmol), allyl acetate (0.8 mmol), $ZnMe_2$ (0.24 mmol), MeCN (2 mL). [d] Reaction performed on 0.1 mmol scale. **c,** Current limitations of alkene 1,2-allylalkylation.

We were pleased to find that in addition to saccharin, a variety of common heterocycles such as phthalimide (**5a**), pyridone (**5b**), quinolones (**5c–d**), pyridazinones (**5e–f**), pyrazoles (**5g–l**), triazoles (**5m–p**),

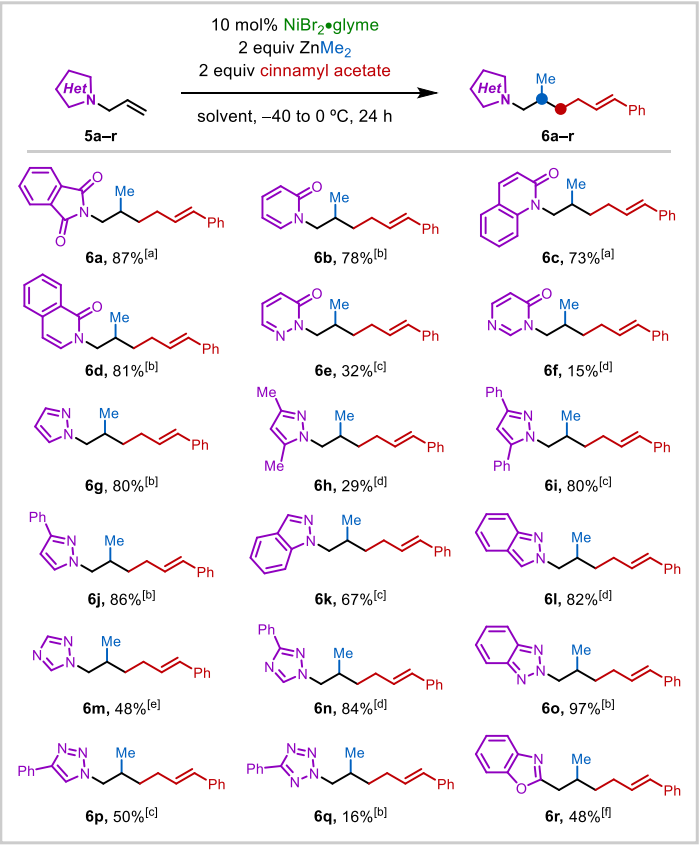


Figure 3. Heterocycle scope of 1,2-allylmethylation method. Reaction conditions: **5a–r** (0.2 mmol), $NiBr_2$(glyme) (0.02 mmol), cinnamyl acetate (0.4 mmol), $ZnMe_2$ (0.4 mmol), solvent (0.6 mL). [a] 2-MeTHF as solvent. [b] THF as solvent. [c] DMF as solvent. [d] Cyclopentylmethylether (CPME) as solvent. [e] Et_2O as solvent. [f] DCM as solvent (1.2 mL).

tetrazole (**5q**), and benzoxazole (**5r**) with differing substitutions on the heteroaromatic rings were also competent directing groups, allowing access to an array of diverse heterocycle-containing products (Figure 3). In many cases, these heterocycles could not be conveniently accessed from the corresponding amine that is formed upon saccharin deprotection, which illustrates the importance of being able to direct via different classes of heterocycles. With each heterocycle we observed that the reaction yield depended on solvent choice. Thus, brief solvent optimization was performed to identify conditions that gave good to excellent yields for these substrates.

Upon scaling up the 1,2-allylmethylation reaction using *N*-allyl saccharin as substrate and cinnamyl acetate as electrophile, we obtained 1.7 grams (95% yield) of product **2f**, displaying the robust nature of this reaction. The saccharin group can be conveniently deprotected to give the free amine, which was isolated following a routine Boc protection (Figure 4a). If desired, saccharin can be partially cleaved to give the ortho-carboxamide substituted arylsulfonamide (**7b**). Moreover, the resulting alkene is amenable to a variety of diversifications as shown in Figure 4b. Specifically, we were able to perform a series of alkene functionalization reactions, including epoxidation (**7c**), Sharpless dihydroxylation (**7d**), Simmons–Smith cyclopropanation (**7e**), Mukaiyama hydration (**7f**), hydrogenation (**7g**), and ozonolysis (**7h**).

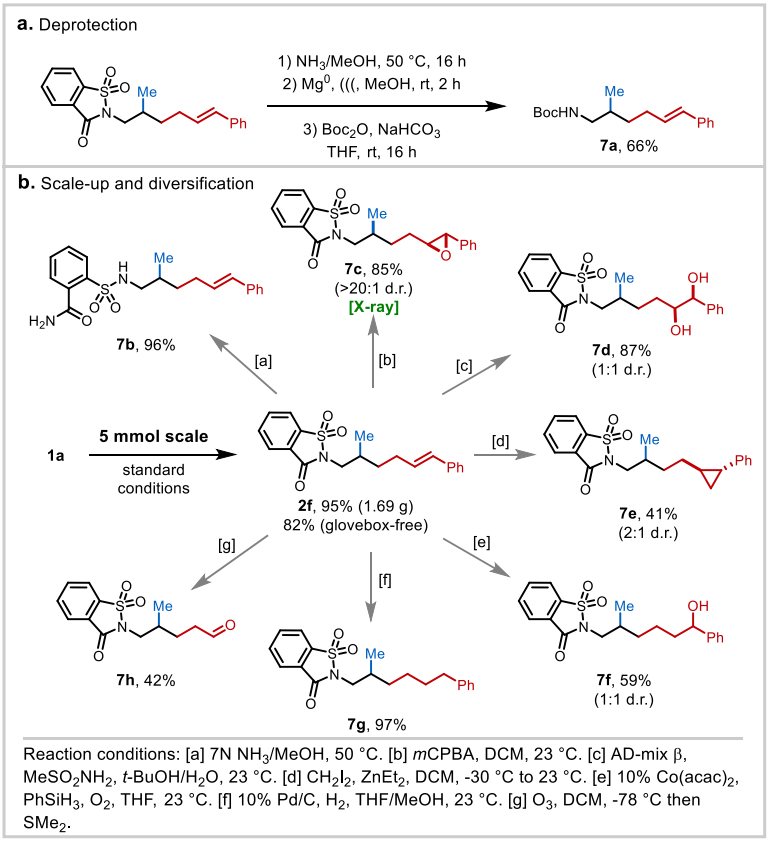


Figure 4. Scale-up and diversification of allylmethylation reaction. **a**, mild deprotection of saccharin directing group to give Boc-protected amine. **b**, synthesis of **1a** on 5 mmol scale and subsequent seven different diversification reactions.

To better grasp the mechanistic underpinnings of this reaction, we performed a series of experiments (Figure 5a and b). First, we utilized *Z*-cinnamyl acetate as electrophile and observed formation of a roughly 2:1 *E*:*Z* product ratio (compounds **2f** and **2f'**, respectively). This result indicates that the proposed nickel π-allyl species is likely able to undergo isomerization under the reaction conditions. In order to rule out the possibility that isomerization occurs after initial formation of the *Z*-product, we prepared separately the predominantly *Z*-product **2f'** (1:8 *E*:*Z*), subjected it to the reaction

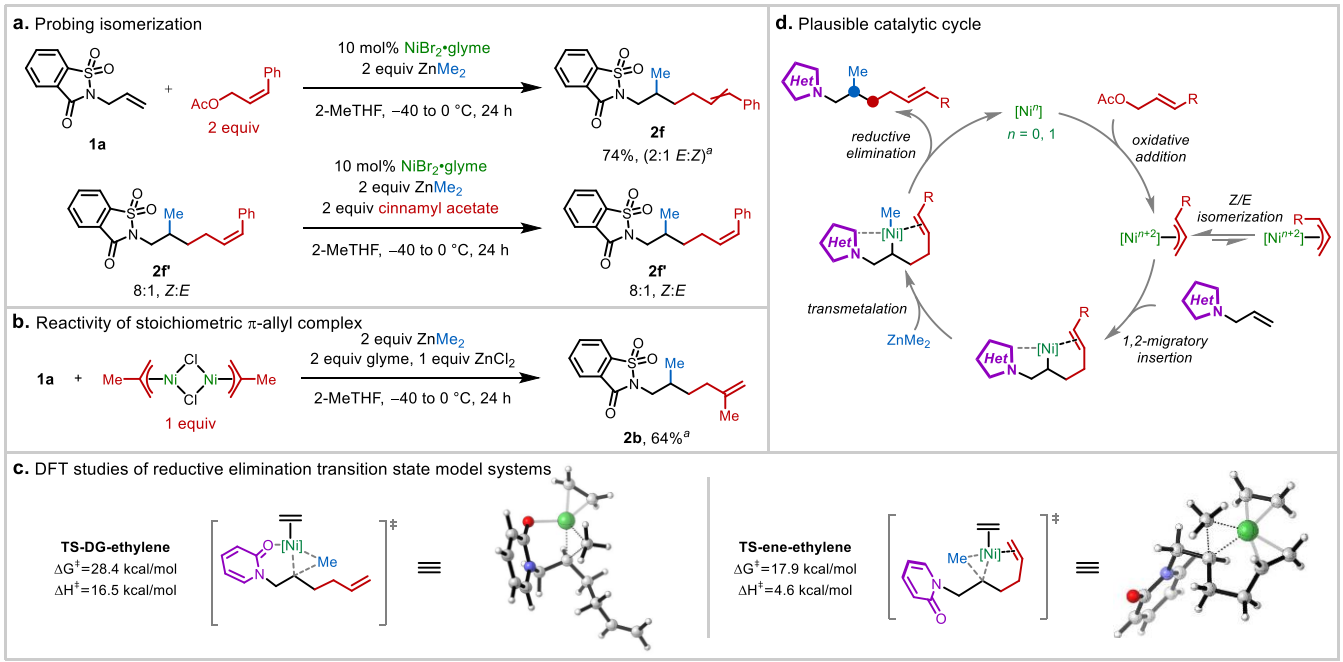


Figure 5. Mechanistic studies and plausible catalytic cycle. **a**, *E*/*Z* isomerization of *Z*-allyl electrophile and control experiment ruling out product isomerization. **b**, Stochiometric reaction of π-allyl-nickel complex shows that it is a competent intermediate. **c**, DFT calculations on a reductive elimination model system reveals that allyl-assisted reductive elimination is energetically preferred. **d**, Plausible catalytic cycle that is consistent with existing data.

conditions, and observed no isomerization of *Z*-**2f'** to *E*-**2f**. When a stoichiometric amount of the methallyl nickel(II) chloride dimer complex **8** was used in place of the nickel catalyst and allyl electrophile, we were able to observe 64% of **2b** by ^{1}H-NMR, showing that the proposed nickel π-allyl species is a competent intermediate. Although mechanistic experiments involving radical inhibitors were performed, the results were inconclusive (See SI).

Based on these results, we propose the catalytic cycle as depicted in Figure 5d, where oxidative addition of an allyl electrophile gives a nickel π-allyl species, which may undergo isomerization from *Z* to *E*. This nickel complex can then bind the substrate and undergo 1,2-migratory insertion of the allyl group to give a new alkyl-nickel species. Transmetallation then occurs to give a doubly chelation-stabilized dialkyl-nickel species. At this stage, dissociation of either the alkene or the heterocycle must take place in order to allow the two alkyl groups to be in a *cis* orientation prior to C(sp^3)–C(sp^3) reductive elimination, which gives the desired allylmethylation product. To probe which of the two possibilities was more likely, we performed computational analysis using density functional theory (DFT) (Figure 5c). Substrate **5b** was used as model reactant since in this case the directing group has only one possible coordination site. Ethylene was used as a representative of all alkene moieties in solution to take over the vacant coordination site. The computed transition state for reductive elimination with alkene coordinated (**TS-ene-ethylene**) is 10.5 kcal/mol lower in energy than the carbonyl-bound transition state (**TS-DG-ethylene**) (see SI for details), consistent with previous reports that have documented the effectiveness of alkene ligands for this purpose.[28,41–47] (Although we believe this pathway to be the most likely, alternative mechanisms cannot be excluded and are depicted in the SI.)

In conclusion, we have demonstrated the compatibility of allyl electrophiles in conjunctive alkene cross-coupling. In particular, we developed a nickel-catalyzed regioselective 1,2-allylmethylation reaction of a variety of *N*-allyl heterocycles that proceeds under mild conditions without the need for an external ligand. The reaction tolerates a wide scope of allyl electrophiles with electron donating, electron withdrawing, and sterically encumbering substituents. It is shown that alkynes may be difunctionalized under similar conditions. Notably, diverse heterocycles such as phthalimide, pyridone, quinolone, pyridazinone, pyrazole, triazole, tetrazole, and benzoxazole are also tolerated and enable the regioselective functionalization of adjacent unactivated alkenes. The

versatility of the resulting products for downstream modification is showcased in two deprotections and six alkene diversification reactions.

References and Notes:

1. Trost, B. M. & Crawley, M. L. Asymmetric Transition-Metal-Catalyzed Allylic Alkylations: Applications in Total Synthesis. *Chem. Rev.* **103**, 2921–2943 (2003).

2. Trost, B. M. Metal Catalyzed Allylic Alkylation: Its Development in the Trost Laboratories. *Tetrahedron* **71**, 5708–5733 (2015).

3. Butt, N. A. & Zhang, W. Transition Metal-Catalyzed Allylic Substitution Reactions with Unactivated Allylic Substrates. *Chem. Soc. Rev.* **44**, 7929–7967 (2015).

4. Mohr, J. T. & Stoltz, B. M. Enantioselective Tsuji Allylations. *Chem. Asian J.* **2**, 1476–1491 (2007).

5. Weaver, J. D., Recio, A., III, Grenning, A. J., & Tunge, J. A. Transition Metal-Catalyzed Decarboxylative Allylation and Benzylation Reactions. *Chem. Rev.* **111**, 1846–1913 (2011).

6. Yanagisawa, A., Nomura, N., Habaue, S. & Yamamoto, H. Nickel-Catalyzed Regioselective Allylation of Allylic Alcohols. *Tetrahedron Lett.* **30**, 6409–6412 (1989).

7. Nomura, N. & RajanBabu, T. V. Nickel-Catalyzed Asymmetric Allylation of Alkyl Grignard Reagents. Effect of Ligands, Leaving Groups and a Kinetic Resolution with a Hard Nucleophile. *Tetrahedron Lett.* **38**, 1713–1716 (1997).

8. Lee, K., Lee, J. & Lee, P. H. Highly Efficient Allyl Cross-Coupling Reactions of Allylindiums with Organic Electrophiles. *J. Org. Chem.* **67**, 8265–8268 (2002).

9. Chen, H., Jia, X., Yu, Y., Qian, Q. & Gong, G. Nickel-Catalyzed Reductive Allylation of Tertiary Alkyl Halides with Allylic Carbonates. *Angew. Chem., Int. Ed.* **56**, 13103–13106 (2007).

10. Son, S. & Fu, G. C. Nickel-Catalyzed Asymmetric Negishi Cross-Couplings of Secondary Allylic Chlorides with Alkylzincs. *J. Am. Chem. Soc.* **130**, 2756–2757 (2008).

11. Sumida, Y., Hayashi, S., Hirano, K., Yorimitsu, H. & Oshima, K. Nickel-Catalyzed Allylation of Allyl Carbonates with Homoallyl Alcohols via Retro-Allylation Providing 1,5-Hexadienes. *Org. Lett.* **10**, 1629–1632 (2008).

12. Stokes, B. J., Opra, S. M. & Sigman, M. S. Palladium-Catalyzed Allylic Cross-Coupling Reactions of Primary and Secondary Homoallylic Electrophiles. *J. Am. Chem. Soc.* **134**, 11408–11411 (2012).

13. Cui, X., Wang, S., Zhang, Y., Deng, W., Qian, Q. & Gong, H. Nickel-Catalyzed Reductive Allylation of Aryl Bromides and Allylic Acetates. *Org. Biomol. Chem.* **11**, 3094–3097 (2013).

14. Srinivas, H. D., Zhou, Q. & Watson, M. P. Enantiospecific, Nickel-Catalyzed Cross-Couplings of Allylic Pivalates and Arylboroxines. *Org. Lett.* **16**, 3596–3599 (2014).

15. Hojoh, K., Shido, Y., Nagao, K., Mori, S., Ohmiya, H. & Sawamura, M. Copper-Catalyzed Enantioselective Allylic Cross-Coupling with Alkylboranes. *Tetrahedron* 2015, 71, 6519–6533.

16. Yang, B. & Wang, Z.-X. Nickel-Catalyzed Cross-Coupling of Allyl Alcohols with Aryl- or Alkenylzinc Reagents. *J. Org. Chem.* **82**, 4542–4549 (2017).

17. Hofstra, J. L., Cherney, A. H., Ordner, C. M., & Reisman, S. E. Synthesis of Enantioenriched Allylic Silanes via Nickel-Catalyzed Reductive Cross-Coupling. *J. Am. Chem. Soc.* **140**, 139–142 (2018).

18. Jia, X.-G., Guo, P., Duan, J. & Shu, X.-Z. Dual Nickel and Lewis Acid Catalysis for Cross-Electrophile Coupling: The Allylation of Aryl Halides with Allylic Alcohols. *Chem. Sci.* **9**, 640–645 (2018).

19. Lan, Y., Yang, F. & Wang, C. Synthesis of gem-Difluoroalkenes via Nickel-Catalyzed Allylic Defluorinative Reductive Cross-Coupling. *ACS Catal.* **8**, 9245–9251 (2018).

20. Derosa, J., Tran, V. T., van der Puyl, V. A. & Engle, K. M. Carbon−Carbon π-Bonds as Conjunctive Reagents in Cross-Coupling. *Aldrichimica Acta* **51**, 21−32 (2018).

21. Giri, R. & KC, S. Strategies toward Dicarbofunctionalization of Unactivated Olefins by Combined Heck Carbometalation and Cross-Coupling. *J. Org. Chem.* **83**, 3013−3022 (2018).

22. Qin, T. *et al.* A General Alkyl-Alkyl Cross-Coupling Enabled by Redox-Active Esters and Alkylzinc Reagents. *Science* **352**, 801−805 (2016).

23. Gu, J.-W., Min, Q.-Q., Yu, L.-C. & Zhang, X. Tandem Difluoroalkylation-Arylation of Enamides Catalyzed by Nickel. *Angew. Chem., Int. Ed.* **55**, 12270−12274 (2016).

24. García-Dominguez, A., Li, Z., & Nevado, C. Nickel-Catalyzed Reductive Dicarbofunctionalization of Alkenes. *J. Am. Chem. Soc.* **139**, 6835−6838 (2017).

25. Gao, P., Chen, L.-A. & Brown, M. K. Nickel-Catalyzed Stereoselective Diarylation of Alkenylarenes. *J. Am. Chem. Soc.* **140**, 10653–10657 (2018).

26. Derosa, J., Tran, V. T., Boulous, M. N., Chen, J. S. & Engle, K. M. Nickel-Catalyzed β,γ-Dicarbofunctionalization of Alkenyl Carbonyl Compounds via Conjunctive Cross-Coupling. *J. Am. Chem. Soc*. **139**, 10657–10660 (2017).

27. Derosa, J., van der Puyl, V. A., Tran, V. T., Liu, M. & Engle, K. M. Directed Nickel-Catalyzed 1,2-Dialkylation of Alkenyl Carbonyl Compounds. *Chem. Sci*. **9**, 5278–5283 (2018).

28. Derosa, J., Kleinmans, R., Tran, V. T., Karunananda, M. K., Wisniewski, S. R., Eastgate, M. D. & Engle, K. M. Nickel-Catalyzed 1,2-Diarylation of Simple Alkenyl Amides. *J. Am. Chem. Soc*. **140**, 17878–17883 (2018).

29. Shrestha, B., Basnet, P., Dhungana, R. K., KC, S., Thapa, S., Sears, J. M. & Giri, R. Ni-Catalyzed Regioselective 1,2-Dicarbofunctionalization of Olefins by Intercepting Heck Intermediates as Imine-Stabilized Transient Metallacycles. *J. Am. Chem. Soc.* **139**, 10653−10656 (2017).

30. Li, W., Boon, J. K. & Zhao, Y. Nickel-Catalyzed Difunctionalization of Allyl Moieties using Organoboronic Acids and Halides with Divergent Regioselectivities. *Chem. Sci.* **9**, 600−607 (2018).

31. Basnet, P., KC, S., Dhungana, R. K., Shrestha, B., Boyle, T. J. & Giri, R. Synergistic Bimetallic Ni/Ag and Ni/Cu Catalysis for Regioselective γ,δ-Diarylation of Alkenyl Ketimines: Addressing β-H Elimination by in situ Generation of Cationic Ni(II) Catalysts. *J. Am. Chem. Soc.* **140**, 15586−15590 (2018).

32. Thapa, S., Dhungana, R. K., Magar, R. T., Shrestha, B., KC, S. & Giri, R. Ni-Catalysed Regioselective 1,2-Diarylation of Unactivated Olefins by Stabilized Heck Intermediates as Pyridylsilyl-Coordinated Transient Metallacycles. *Chem. Sci.* **9**, 904−909 (2018).

33. Zhao, X., Tu, H.-Y., Guo, L., Zhu, S., Qing, F.-L. & Chu, L. Intermolecular Selective Carboacylation of Alkenes via Nickel-Catalyzed Reductive Radical Relay. *Nat. Commun.* **9**, 3488 (2018).

34. Semba, K., Ohta, N., Yano, Y. & Nakao, Y. Carboallylation of Electron-Deficient Alkenes by Palladium/Copper Catalysis. *Chem. Commun.* **54**, 11463–11466 (2018).

35. Semba, K., Ohta, N. & Nakao, Y. Carboallylation of Electron-Deficient Alkenes with Organoboron Compounds and Allylic Carbonates by Cooperative Palladium/Copper Catalysis. *Org. Lett.* **21**, 4407–4410 (2019).

36. Gallazzi, M. C., Hanlon, T. L., Vitulli, G. & Porri, L. Stereochemistry of the Insertion Reaction of Norbornene into a Nickel-allyl and a Palladium-allyl Bond. *J. Organomet. Chem.* **33**, C45 (1971).

37. Chiusoli, G. P. Catalysis of Olefin and Carbon Monoxide Insertion Reactions. *Acc. Chem. Res.* **6**, 422 (1973).

38. Chiusoli, G. P., Salerno, G. & Dallatomasina, F. Transition Metal-Catalysed Rearrangement of Allyl But-3-enoate to Hepta-2,6-dienoic or Hepta-3,6-dienoic Acids. *J. Chem. Soc., Chem. Commun.* 793 (1977).

39. Catellani, M., Chiusoli, G. P., Dradi, E. & Salerno, G. Nickel-catalyzed Allylation of Norbornene. *J. Organomet. Chem.* 177, C29 (1979).

40. van der Puyl, V. A., Derosa, J. & Engle, K. M. Directed, Nickel-Catalyzed Umpolung 1,2-Carboamination of Alkenyl Carbonyl Compounds. *ACS Catal.* **9**, 224–229 (2019).

41. Giovannini, R., Stüdemann, T., Dussin, G., & Knochel, P. An Efficient Nickel-Catalyzed Cross-Coupling between sp^3 Carbon Centers. *Angew. Chem., Int. Ed.* **37**, 2387–2390 (1998).

42. Giovannini, R. & Knochel, P. Ni(II)-Catalyzed Cross-Coupling between Polyfunctional Arylzinc Derivatives and Primary Alkyl Iodides. *J. Am. Chem. Soc.* **120**, 11186–11187 (1998).

43. Giovannini, R., Stüdemann, T., Devasagayaraj, A., Dussin, G., & Knochel, P. New Efficient Nickel-Catalyzed Cross-Coupling Reaction between Two Csp^3 Centers. *J. Org. Chem.* **64**, 3544–3553 (1999).

44. Jensen, A. E. & Knochel, P. Nickel-Catalyzed Cross-Coupling between Functionalized Primary or Secondary Alkylzinc Halides and Primary Alkyl Halides. *J. Org. Chem.* **67**, 79–85 (2002).

45. Huang, C.-Y. & Doyle, A. G. Nickel-Catalyzed Negishi Alkylations of Styrenyl Aziridines. *J. Am. Chem. Soc.* **134**, 9541–9544 (2012).

46. Nielsen, D. K., Huang, C.-Y. & Doyle, A. G. Directed Nickel-Catalyzed Negishi Cross Coupling of Alkyl Aziridines. *J. Am. Chem. Soc.* **135**, 13605–13609 (2013).

47. Huang, C.-Y. & Doyle, A. G. Electron-Deficient Olefin Ligands Enable Generation of Quaternary Carbons by Ni-Catalyzed Cross-Coupling. *J. Am. Chem. Soc.* **137**, 5638–5641 (2015).

48. Yan, G., Borah, A. J., Wang, L. & Yang, M. Recent Advances in Transition Metal-Catalyzed Methylation Reactions. *Adv. Synth. Catal.* **357**, 1333–1350 (2015).

49. Greene, M. A., Yonova, I. M., Williams, F. J. & Jarvo, E. R. Traceless Directing Group for Stereospecific Nickel-Catalyzed Alkyl-Alkyl Cross-Coupling Reactions. *Org. Lett.* **14**, 4293–4296 (2012).

50. Bao, X., Yokoe, T., Ha, T. M., Wang, Q. & Zhu, J. Copper-catalyzed Methylative Difunctionalization of Alkenes. *Nat. Commun.* **9**, 3725–3732 (2018).

51. Wilsily, A., Tramutola, F., Owston, N. A. & Fu, G. C. New Directing Groups for Metal-Catalyzed Asymmetric Carbon–Carbon Bond-Forming Processes: Stereoconvergent Alkyl–Alkyl Suzuki Cross-Couplings of Unactivated Electrophiles. *J. Am. Chem. Soc.* **134**, 5794–5797 (2012).

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