Sulfonamide Directivity Enables Ni-Catalyzed 1,2-Diarylation of Diverse Alkenyl Amines

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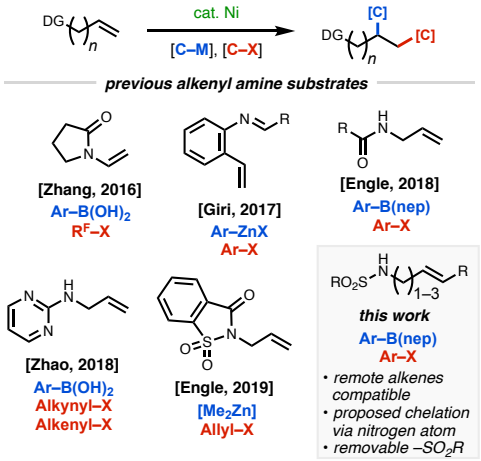
ABSTRACT: 1,2-Diarylation of alkenyl sulfonamides with aryl iodides and aryl boronic esters under nickel catalysis is reported. The developed method tolerates coupling partners with disparate electronic properties and substitution patterns. Di- and trisubstituted alkenes, as well as alkenes distal from the directing group, are all accommodated. Control experiments are consistent with a N–Ni coordination mode of the directing group, which stands in contrast to earlier reports on amide-directed 1,2-diarylation that involve carbonyl coordination. The synthetic utility of the method arises from the dual function of the sulfonamide as both a directing group and masked amine nucleophile. This is highlighted by various product diversifications where complex amine compounds are synthesized in a two-step sequence of *N*-functionalization and deprotection of the sulfonyl group.

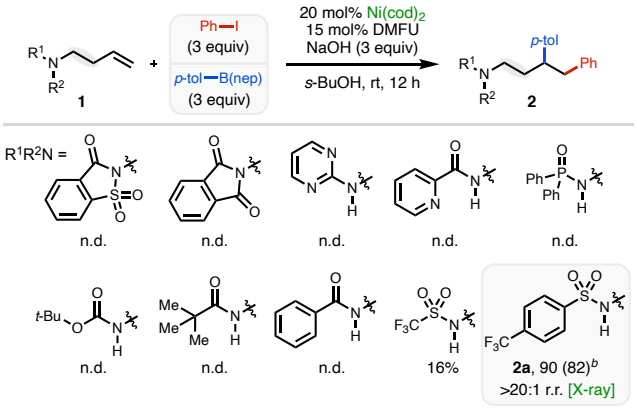
KEYWORDS: *Alkene, diarylation, nickel, sulfonamide, directing group*

Forging contiguous C–C bonds through 1,2-dicarbofunctionalization of alkenes, also referred to as conjunctive cross-coupling, has blossomed into a vibrant area of catalysis that leverages the unique reactivity of diverse transition metals, including Pd, Ni, Co, Cu, and Fe.[1a-b] In this context, nickel provides unique advantages compared to other transition metals, such as palladium, by having a higher propensity toward oxidative addition and 1,2-migratory insertion steps while being more resilient towards β-hydride elimination.[1c] 1,2-Dicarbofunctionalization of alkenyl amine substrates, wherein a protected amine directs key steps in the catalytic cycle, is an attractive approach for selectivity control and offers rapid entry to functionalized alkyl amine product libraries. 1,2-(Fluoroalkyl)arylation and 1,2-diarylation of electronically activated enamides and ortho-vinyl aniline derivatives have been reported by Zhang[2a] and Giri[2d], respectively (Scheme 1). More recently the use of a non-removable pyrimidyl auxiliary that facilitates the 1,2-dicarbofunctionalization of non-conjugated terminal alkenes via coordination of Ni with a N(sp^2) atom center was reported by Zhao and coworkers.[2e] Our group has reported the 1,2-diarylation and 1,2-allylmethylation of simple alkenyl amides and *N*-allyl heterocycles, respectively.[3a-b] Ni-catalyzed conjunctive cross-couplings of various classes of non-conjugated alkenes have been reported by other research groups via different mechanistic paradigms.[4] This progress notwithstanding, significant limitations remain in this family of transformations. In particular, existing methods are incompatible with homoallyl and bis-homoallyl amines as well as internal alkenyl amine substrates. Moreover, the directing groups employed in earlier reports are synthetically restrictive in that they cannot be directly employed in further functionalization. The goal of the present study was to identify an amine-based directing group capable of promoting 1,2-diarylation of remote, highly substituted alkenes and engaging in diverse downstream *N*-functionalization chemistry, which would allow alkenyl amines to act as linchpins in modular synthesis. To this end, herein we report the identification of sulfonamides as uniquely effective and versatile[5,6] directing groups in 1,2-diarylation of alkenes under nickel/dimethyl fumarate (DMFU) catalysis.[7]



Scheme 1. Previous reports and synopsis of new findings.

Table 1. Optimization of 1,2-diarylation reaction.[a]

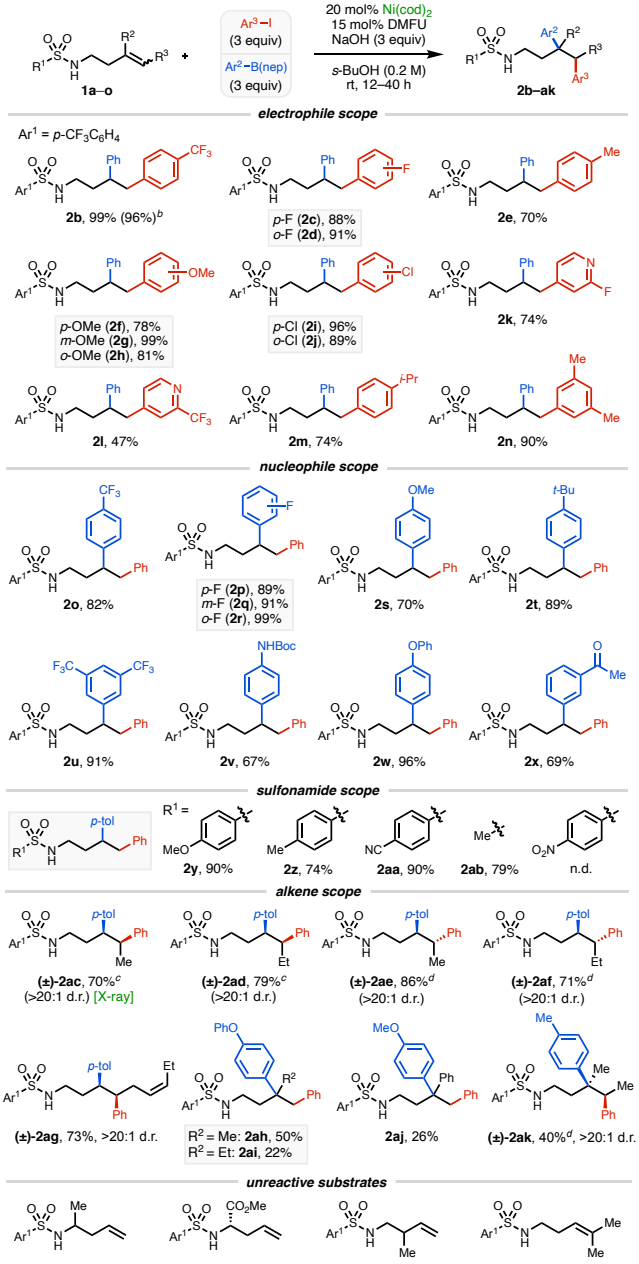


entry	deviation from standard conditions	%Yield **2a**[c]
1	no ligand	30
2	*p*-tol-B(OH)$_2$ instead of *p*-tol-B(nep)	54
3	*p*-tol-B(pin) instead of *p*-tol-B(nep)	50
4	Ph-Br instead of Ph-I	n.d.
5	Ni(cod)(DQ), NiCl$_2$, Ni(acac)$_2$, or NiBr$_2$•glyme instead of Ni(cod)$_2$	n.d.
6	conditions from alkenyl amide diarylation[d]	60
7	conditions from alkenyl carboxylate diarylation[e]	n.d.
8	10 mol% Ni(cod)$_2$ instead of 20 mol%	90
9	1.5 equiv of PhI, *p*-tolB(nep), NaOH instead of 3 equiv	90

[a]Reaction conditions: **1a** (0.1 mmol), *s*-BuOH (0.2 M). [b]Values in parentheses are isolated yields. [c]Percentage yield by ^{1}H NMR using CH_2Br_2 as the internal standard; n.d. = not detected. [d]Reaction conditions: 15 mol% Ni(cod)$_2$, 15 mol% dimethylfumarate, 1.5 equiv ArI, 1.5 equiv ArB(nep), 2 equiv NaOH, *i*-BuOH (0.2 M) at r.t. [e]Reaction conditions: 15 mol% Ni(cod)$_2$, 2 equiv ArI, 2 equiv ArB(nep), 2 equiv NaOH, *s*-BuOH (0.1 M) at 50 °C.

To commence the study, we selected iodobenzene and 4-tolylboronic acid neopentyl glycol ester (p-tolB(nep)) as model coupling partners and systematically surveyed homoallyl amine substrates bearing different protecting groups (Table 1).[2e, 3a-b] Benzoylsulfonyl, phthaloyl, pyrimidyl, 2-picolinoyl, and diphenylphosphinic protecting groups did not promote 1,2-diarylation.[8] Carbonyl groups that were previously found to direct 1,2-diarylation of allylamine substrates, namely Boc-, Piv-, and Bz-, were ineffective in this case with a more distal alkene. We next turned to sulfonyl protecting groups[6] with the hypothesis that in this case, the nickel catalyst may bind the sulfonamide through nitrogen. Gratifyingly, triflyl-protected homoallyl amine gave the desired product, albeit in low yield. Moving to a less electron-withdrawing aryl sulfonyl group provided 1,2-diarylated product **2a** in excellent yield and regioselectivity, and its connectivity was confirmed by single-crystal X-ray diffraction. While various aryl sulfonamide directing groups were similarly effective (vide infra), the 4-(trifluoromethyl)-phenyl group provided a convenient ^{19}F NMR handle for reaction analysis and was employed for much of the ensuing work. The absence of DMFU and employment of the aryl boronic acid and pinacol ester resulted in diminished yields, showing the importance of DMFU in facilitating reductive elimination (Entries 1–3).[7] Bromobenzene was unreactive as an electrophile, and other nickel precatalysts, such as Ni(cod)(DQ), NiCl$_2$, Ni(acac)$_2$, and NiBr$_2$•glyme, were

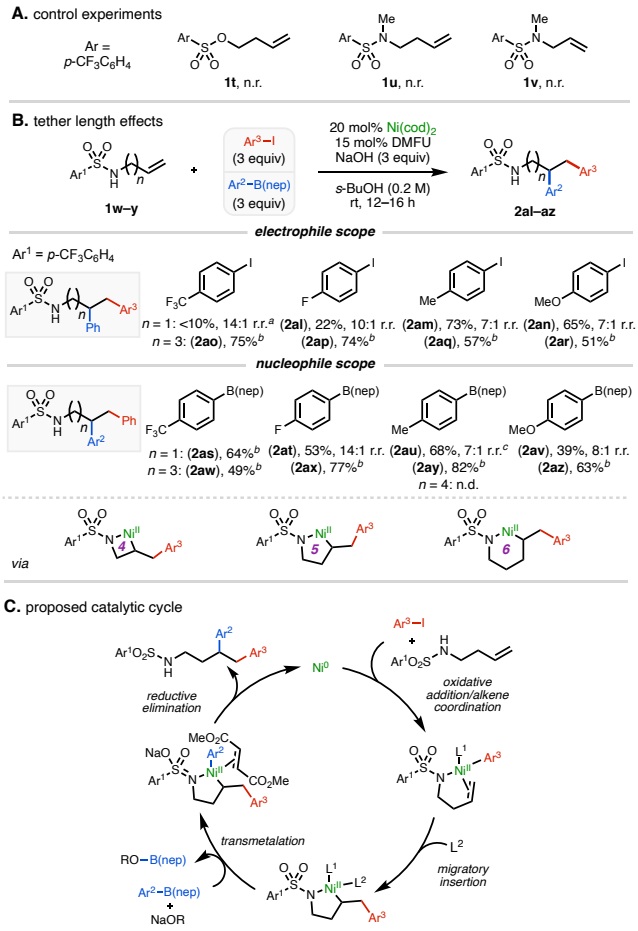
Table 2. Electrophile, Nucleophile, Sulfonamide, and Alkene Scope.[a]



[a]Reactions performed on 0.1 mmol scale. [b]Reactions performed on 1 mmol scale. Percentages represent isolated yields. [c]Product was synthesized from (*Z*)-alkene. [d]Product was synthesized from (*E*)-alkene.

ineffective (Entries 4–5). Under previously published reaction conditions for diarylation of alkenyl amide substrates, lower yield was obtained (Entry 6). No diarylation was observed under conditions for alkenyl carboxylate substrates (Entry 7).[3a,4i] While excellent yields were obtained when lower catalyst loading or equivalents of coupling partners and base were used with the standard substrate (Entry 8–9), other examples required higher loading and equivalents to obtain high yields.

Next, the scope of electrophilic and nucleophilic aryl coupling partners was investigated (Table 2). Electron-

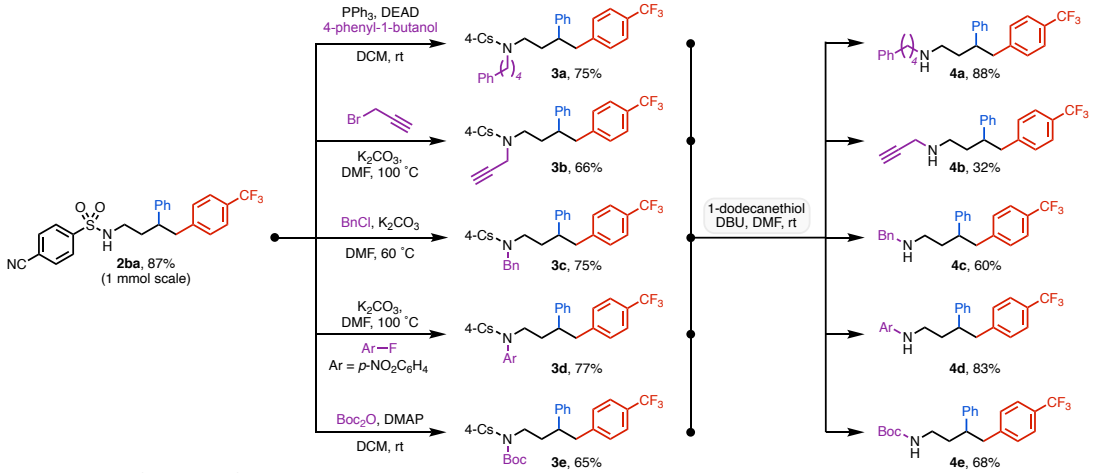


Scheme 2. (A) Control experiments to test sulfonamide and nitrogen importance. (B) Tether length effects on 1,2-diarylation. [a]Percentage yield by ^{1}H NMR using CH_2Br_2 as the internal standard. [b]Product isolated as a single regioisomer (>20:1). [c]Product connectivity was confirmed by single-crystal X-ray diffraction. (C) Proposed catalytic cycle having directing group with X-type coordination upon migratory insertion. L^1 and L^2 represent neutral donors including DMFU, alkene substrate, solvent, etc.

withdrawing groups at the *para* position of the aryl iodides afforded the highest product yields (**2b–c**, **2i**), and the product yield decreased with electron-neutral and -donating groups (**2e–f**, **2m**). It is worth noting that product **2b** was synthesized in an excellent yield on a larger scale (1 mmol, 0.48 g isolated). Electron-withdrawing groups on the *meta* position of the aryl iodides gave no 1,2-diarylated product; however, electron-donating groups (**2g**, **2n**) gave 1,2-diarylation in excellent yields. *Ortho*-substituted electron-withdrawing or donating groups on the aryl iodide had little effect on the product yield in comparison to the *para*-substituted examples (**2d**, **2h**, **2j**). Consistent with the previously discussed results, electron-deficient 2-fluoro-4-iodopyridine gave good yield (**2k**) while 4-iodo-2-(trifluoromethyl)pyridine gave a moderate yield (**2l**). With regards to the nucleophile scope, no apparent trend is observed. Electron-withdrawing and weakly electron-donating groups on the *para* position (**2o–p**, **2t**) gave very good yields. Product yields greatly varied with the use of electron-donating groups on the *para* position ranging from moderate to excellent yields (**2s**, **2v–w**). Aryl boronic esters with electron withdrawing groups on the *meta* and *ortho* positions (**2q**, **2r**, **2u**, **2x**) resulted in moderate to excellent yields as well.

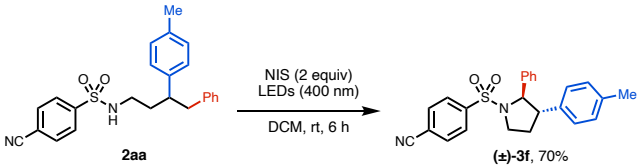
Next, we varied the aryl sulfonyl group by substitution of the trifluoromethyl moiety at the *para*-position and observed good to excellent yields (**2y–aa**). Mesyl (Ms) protected homoallyl amine **2ab** is a competent substrate under the reaction conditions. However, product was not detected in the case of a nosyl protecting group, which we attribute to the potential inhibitory effect of nitro groups on Ni catalyst activity.[9] We then examined alkene substrates that are typically challenging in 1,2-diarylation. Pleasingly, (*Z*)- and (*E*)-internal alkenes were well tolerated under the optimized reaction conditions. Diarylated products (**(±)-2ac–ad**) from two 1,2-disubstituted (*Z*)-alkenes were obtained in good yields and as single diastereomers, as confirmed by single-crystal X-ray diffraction. Several 1,2-disubstituted (*E*)-alkenes were also successfully diarylated in good yields (**(±)-2ae–ag**). In addition, various 1,1-disubstituted terminal alkenes were found to afford product in low to moderately good yields under the reaction conditions (**2ah-aj**). To our delight, diarylated product **(±)-2ak** was obtained in moderate yield as a single diastereomer from the trisubstituted (*E*)-alkene. With substitution at the α- or β-positions, no conversion was observed. A homoprenyl trisubstituted alkenyl sulfonamide proved ineffective in 1,2-diarylation.

In a series of control experiments, homoallyl aryl sulfonate **1t** and *N*-methylated sulfonamides **1u** and **1v** were subjected



Scheme 3. Diversification of 1,2-diarylated products as a linchpin technology. Percentages represent isolated yields.

to the optimized conditions, which resulted in no product formation (Scheme 2A). This indicates that the N–H moiety is important in the transformation. While we were successful in developing a remote alkene 1,2-diarylation reaction, we were curious about the effect of alkene distance on reactivity (Scheme 2B). Both electrophile and nucleophile scopes were examined for the aryl sulfonyl protected allyl and pentenyl amines under the optimized reaction conditions. Electron-deficient aryl iodides gave low yields but good regioselectivity (**2al**) while electron-neutral and donating aryl iodides gave higher yields but lower regioselectivity (**2am–n**) for the protected allyl amine starting material. Both electron-deficient and electron-donating aryl iodides gave moderate to good yields with excellent regioselectivity for the protected pentenyl amine starting material (**2ao–ar**). For the nucleophile scope, electron-deficient boronic esters gave the desired product in good yields with excellent regioselectivity (**2as–at**), while electron-neutral and electron-donating nucleophiles resulted in lower yields with lower regioselectivity (**2au–av**) for the protected allyl amine substrate. Moderate to excellent yields and exceptional regioselectivity were obtained with the protected pentenyl amine substrate (**2aw–2az**). Extension of the alkenyl chain to aryl sulfonyl protected hexenyl amine gave no product. We hypothesize that these alkenyl amine substrates proceed through 4–6-membered N-boundnickelacycles,[7c–d] where a 7-membered nickelacycle is unfavorable (Scheme 2B). Though the intermediacy of 6–8-membered O-bound nickelacycles cannot be ruled out, we view this possibility as less likely since tertiary sulfonamides are unreactive in this system. This stands in contrast to our previous report[3a] in which tertiary amides were competent substrates and O-bound intermediates were proposed based on experimental and computational data.



Scheme 4. HLF cyclization of a representative product.

Although this reaction may proceed via a N–Ni coordination mode,[10] the general catalytic cycle likely follows a similar mechanism as that of alkenyl amide and carboxylate diarylation (Scheme 2C).[3a,4i] The proposed catalytic cycle starts with nickel undergoing oxidative addition into the aryl–iodide bond, followed by alkene coordination of the protected alkenyl amine. Migratory insertion proceeds with the formation of a Ni^{II}(alkyl)(sulfonamido) metallacycle. Subsequent transmetalation[11] affords a Ni^{II}(alkyl)(aryl) species which would finally undergo reductive elimination to give the 1,2-diarylated product.[7c–e] It should be noted that this catalytic cycle may also operate with the sulfonamide directing group as an L-type ligand upon migratory insertion and this pathway cannot be ruled out at this time.

We next envisioned that this method could have synthetic applicability as a linchpin technology where the diarylated products could engage in *N*-functionalization followed by deprotection to form highly functionalized secondary amines that would otherwise be difficult to construct. The 4-cyanophenyl sulfonyl (4-Cs) protecting group was utilized in scale-up and diversification efforts due to its precedented ease of removal by use of 1-dodecanethiol.[5] With this in mind, we then synthesized diarylated product **2ba** in 87% yield (1 mmol, 0.40 g isolated) (Scheme 3). This product was then subjected to Mitsunobu coupling, propargylation, benzylation, S_NAr, and Boc protection reactions, which proceeded in moderate to good yields providing a diverse set of *N*-functionalized products (**3a–e**). Subsequent treatment with 1-dodecanethiol and DBU led to the removal of the aryl sulfonyl protecting group affording dialkyl, alkyl propargyl, alkyl benzyl, alkyl aryl, and alkyl Boc-protected amines in low to excellent yields (**4a–e**). Lastly, a violet-light-initiated Hofmann–Löffler–Freytag (HLF) cyclization of a representative product, **2z**, furnished 4-Cs-protected pyrrolidine **(±)-3f** in good yield, with the two aryl groups in a *trans* configuration (Scheme 4).[12]

In summary, a Ni-catalyzed 1,2-diarylation of aryl sulfonyl protected alkenyl amines with aryl iodides and aryl boronic esters was developed. This method tolerates electronically varied aryl coupling partners. Electronics on the aryl sulfonyl protecting group is indiscriminate of its directing capabilities with the exception of nosyl substitution. Internal and 1,1-disubstituted alkenes are competent substrates, affording the desired products in moderate to high yields with excellent regio- and diastereoselectivity. Control experiments showed that the free sulfonamide N–H is essential in the reaction. The alkenyl chain length was determined to tolerate dicarbofunctionalization with aryl sulfonyl protected allyl, butenyl, and pentenyl amines. Finally, this methodology may be implemented as a linchpin technology where aryl sulfonyl protected alkenyl amines could engage in 1,2-diarylation, then *N*-functionalization, and lastly deprotection to afford trifunctionalized secondary amines allowing leeway for facile complex amine synthesis.

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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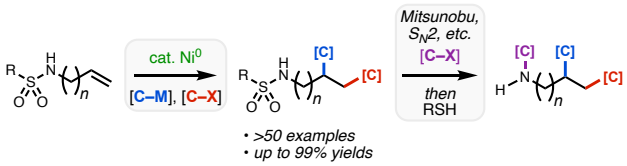
cat. Ni0
[C–M], [C–X]
Mitsunobu,
SN2, etc.
[C–X]
then
RSH
[C]
[C]
[C]
[C]
[C]
• >50 examples
• up to 99% yields