Ni-Catalyzed 1,2-Diarylation of Alkenyl Ketones: A Comparative Study of Carbonyl-Directed Reaction Systems

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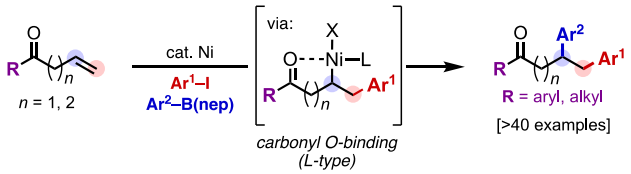
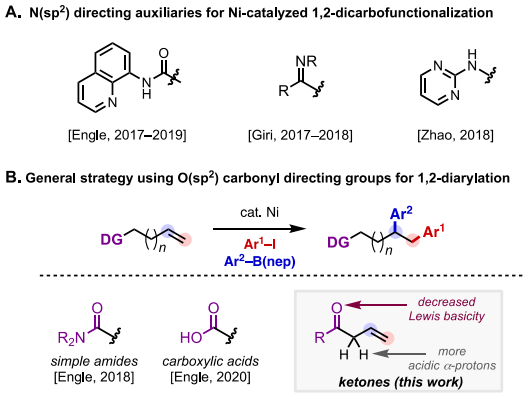


ABSTRACT: A nickel-catalyzed 1,2-diarylation of alkenyl ketones with aryl iodides and arylboronic esters is reported. Ketones with a variety of substituents serve as effective directing groups, offering high levels of regiocontrol. A representative product is diversified into a wide range of useful products that are not readily accessible via existing 1,2-diarylation reactions. Preliminary mechanistic studies shed light on the binding mode of the substrate, and Hammett analysis reveals the effect of electronic factors on initial rates.

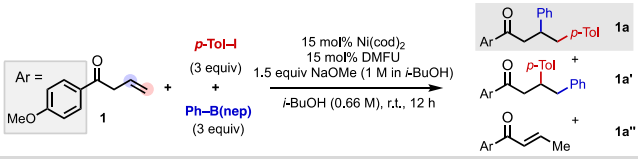
The catalytic addition of two distinct carbogenic fragments across an alkene using a transition metal via conjunctive cross-coupling has recently emerged as a powerful strategy to synthesize complex molecules.[1] In general, reactions of this type involving an initial 1,2-migratory insertion step have historically required conjugated alkene substrates for reactivity and selectivity control.[2] In an effort to bridge this synthetic gap, our group and others have employed directing groups to facilitate 1,2-dicarbofunctionalization of non-conjugated alkenes under nickel catalysis.[3] This concept was

Scheme 1. Background and Synopsis of Current Work.



initially executed using N(sp²)- containing directing auxiliaries that require at least two concession steps for installation and removal, detracting from the practicality of the approach (Scheme 1A).[3a–d] Our laboratory previously demonstrated the use of simple alkenyl amides and carboxylates in nickel-catalyzed 1,2-diarylation reactions (Scheme 1B).[3e,g] Given the complementary

Table 1. Optimization of Reaction Conditions.[a]



entry	deviation from standard conditions	%yield[b]	1a:1a'	%yield 1a"
1	none	83 (77)	10:1	9
2	conditions from alkenyl amide diarylation (Ref. 3e)[c]	8	--	--
3	no $Ni(cod)_2$	n.d.	--	47
4	no Ligand	79	8:1	--
5	SIPr instead of DMFU	59	5:1	2
6	1.5 equiv NaOMe (solid)	63	8:1	--
7	1.5 eq. of PhB(nep) and *p*-Tol–I instead of 3.0 equiv	40	10:1	27
8	$PhB(OH)_2$ instead of PhB(nep)	29	--	--
9	PhB(pin) instead of PhB(nep)	17	--	31
10	*p*-Tol–Br instead of *p*-Tol–I	8	--	25
11	5 mol% $Ni(cod)_2$ instead of 15 mol%	43	9:1	29
12	$NiBr_2$•glyme instead of $Ni(cod)_2$	32	6:1	35
13	$NiCl_2$ or $Ni(acac)_2$ instead of $Ni(cod)_2$	n.d.	--	--
14	Ni(cod)(DMFU) instead of $Ni(cod)_2$	75	10:1	11
15	Ni(cod)(DQ) instead of $Ni(cod)_2$	n.d.	--	42

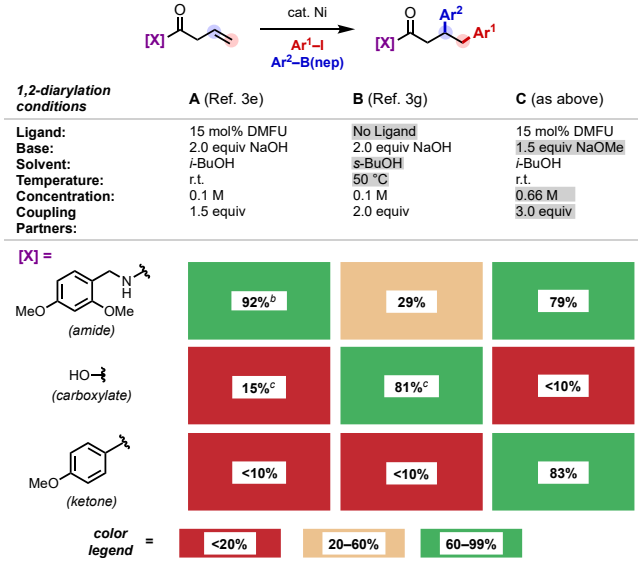
[a]Reaction were performed on a 0.1 mmol scale. Percentages represent ^1H NMR yields using CH_2Br_2 as internal standard; n.d. = not detected. Percentages in parentheses represent isolated yields. Combined yield of **1a** and **1a'**. [c]Reaction conditions: 15 mol% $Ni(cod)_2$, 15 mol% DMFU, 1.5 equiv ArI, 1.5 equiv ArB(nep), 2 equiv NaOH, 0.1 M *i*-BuOH, at r.t.

utility of ketone functional groups in synthesis,[4,5] we sought to extend this regioselective 1,2-diarylation methodology to substrates containing native ketone functional groups, presumably binding the metal through an O(sp^2) atom.[6]

At the same time, we were aware of two potential challenges: 1) the decreased Lewis basicity of the carbonyl lone pair compared to amides and carboxylates, which can impact productive binding to the nickel catalyst in the key migratory insertion step, and 2) increased acidity of the α-C–H bonds, which can lead to undesired isomerization of the alkene substrate. In a series of important previous studies, Giri has established that pre-formed ketimines can effectively engage in conjunctive cross-coupling[7a,b] and that the resulting products can be hydrolyzed to the corresponding ketones. This chemistry is limited to substrates containing unsaturation at the γ,δ-position, presumably due to the highly acidic α-protons that contribute to isomerization in the presence of organozinc nucleophiles, underscoring the difficulty of this type of transformation. Herein, we describe a selective 1,2-diarylation of alkenyl ketone substrates enabled by carefully tuned reaction conditions that minimal alkene isomerization (Scheme 1B).

To initiate our investigation, we elected to use aryl ketone **1** as our standard substrate, with 4-iodotoluene (*p*-Tol–I) and phenylboronic acid neopentyl glycol ester (PhB(nep)) (nep = neopentyl glycolato) as coupling partners, and Ni(cod)$_2$ as the precatalyst with dimethyl fumarate (DMFU) as ligand (Table 1).[8] After extensive optimization and fine-tuning of reaction conditions to minimize isomerization, we were able to identify conditions that delivered 83% combined yield of the two possible regioisomers in 10:1 r.r., with the major product corresponding to electrophile incorporation distal to the directing group (entry 1). We found the addition of NaOMe as a stock so-

Figure 1. Comparison of 1,2-Diarylation Conditions.[a]

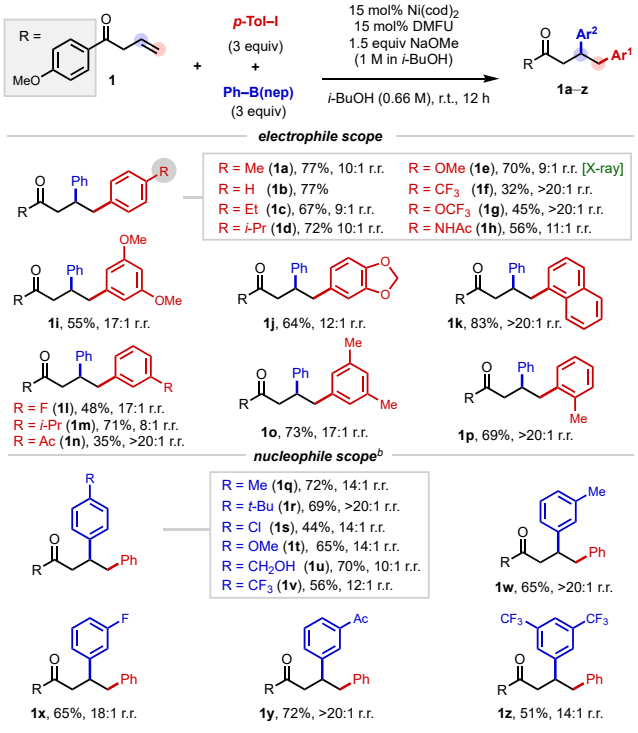


[a]Percentages represent ^{1}H NMR yields using CH_2Br_2 as internal standard. [b]Yield taken from Ref 3e. [c]Yield taken from Ref 3g.

lution to be vital for high yields, presumably owing to the slow dissolution rate of the solid base (entry 6).[9] Under our previously published reaction conditions for simple alkenyl amide substrates, the 1,2-diarylated product(s) could be detected in only 8% yield (entry 2). Interestingly, the reaction proceeded in good yield without an ancillary ligand or with 1,3-bis(2,6-diisopropylphenyl)imidazolidine-2-ylidene (SIPr) instead of DMFU, with SIPr leading to lower regioselectivity (entries 4 and 5). Phenylboronic acid and the corresponding pincaol ester were low-yielding (entries 8 and 9). Encouragingly, $NiBr_2$•glyme was a competent Ni(II) source, giving the desired products in 32% combined yield (entry 12). $NiCl_2$, Ni(acac)$_2$, and Ni(cod)(DQ) (DQ = duroquinone) were found to be ineffective (entries 13 and 15). Pre-ligation of the DMFU did not offer any advantage, with the products furnished in 75% yield when Ni(cod)(DMFU) was used as the precatalyst (entries 14).

At this stage, we sought to compare the optimized conditions in each of our carbonyl-directed 1,2-diarylation reactions to gain a better understanding of the subtle effects of changes to reaction conditions across different substrate classes (Figure 1). In all cases, Ni(cod)$_2$ precatalyst and alcohol solvents were necessary for obtaining high yields. In addition, the superior reactivity of ArB(nep) coupling partners is a shared feature, reflecting its privileged nature in nickel catalysis.[10] Cross-screening of the optimized reaction conditions for various 1,2-diarylation reactions against amide, carboxylate, and ketone substrates, revealed that choice of ligand, base, alcohol solvent, and temperature are key variables in being able to successfully extend this methodology to different substrate classes. For example, the amide substrate requires DMFU as a ligand to bolster the product yield, whereas DMFU has only a minor effect with ketone substrates;[11] added ligand had no bene-

Scheme 2. Electrophile and Nucleophile Scope.[a]



[a]Reactions performed on a 0.1 mmol scale. Percentages represent isolated yields. [b]Reactions were performed in *i*-BuOH

fit in the carboxylate system. Also, less Lewis basic ketones benefited from the use of a NaOMe stock solution, compared to solid NaOMe. Both the amide and ketone substrates work well with *i*-BuOH, whereas *s*-BuOH is essential to the carboxylate substrate. Interestingly, carboxylate substrates are incompati-

ble with the optimal temperature (r.t.) for other classes, presumably owing to the elevated temperatures required to prevent inhibitory carboxylate binding to the nickel catalyst. Collectively, these results illustrate the subtleties of reaction optimization across these systems, whilst providing end users with an idea of what variables to prioritize.

Having identified optimal reaction conditions, we moved on to examine the electrophile scope using PhB(nep) as the nucleophilic coupling partner (Scheme 2).[12] Aryl iodides, bearing electron-donating substituents in the *para*- and *meta*-positions, reacted in good to excellent yields to deliver the desired products with moderate to excellent regioselectivity (**1a–1e**, **1i, 1j, 1l–o**). Aryl iodides with substitution in the *ortho*-position reacted in good to excellent yields, which gave the desired products with excellent regioselectivity (**1k,p**).

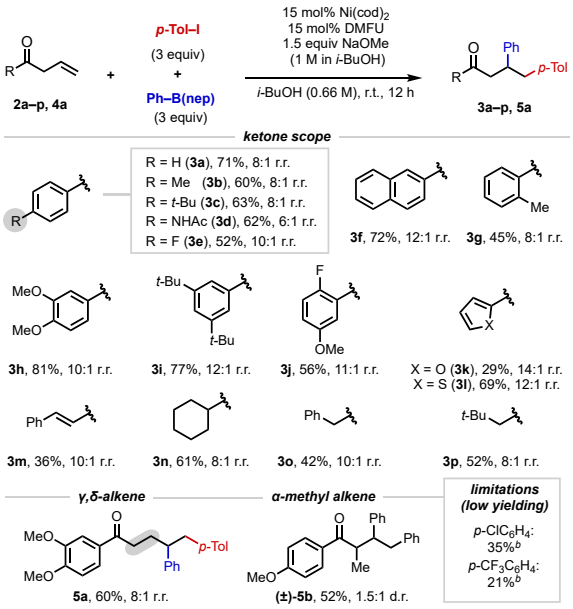
Electron-withdrawing substituents resulted in diminished reactivity, but still delivered the desired products in moderate yields (**1f**,**g**,**l**) with excellent regioselectivity. Notably, aryl iodides containing –NHAc and –Ac groups were compatible in this reaction, allowing for potential downstream modification (**1h**,**n**). It is worth mentioning, that for sterically similar electrophiles, r.r. tends to be lowest for electron-rich aryl iodides and highest for electron-poor aryl iodides. Heteroaryl iodides, 4-iodobenzaldehyde, and 4-iodophenol coupling partners were incompatible under the optimized reaction conditions (see SI). Next, we investigated the scope of the nucleophile in the reaction, using iodobenzene as the electrophilic component. In general, a wide range of electron-rich and electron-poor ArB(nep) coupling partners performed well under optimized conditions, giving the desired products in good to excellent yield (**1q–1z**) with moderate to excellent regioselectivity. Aryl B(nep) coupling partners containing tethered alcohols, –Cl, and –Ac groups were tolerated in moderate to good yields (**1s,u,y**).

We next explored the scope and limitations of this method by testing other representative alkenyl ketones (Scheme 3). Given the simplicity and modularity of synthesizing allyl ketones through a Barbier allylation/oxidation sequence (see SI), we envisioned that this method could serve as a powerful tool for rapid assembly of *β,γ*-diarylated ketones. Indeed, across several different substrates, moderate to excellent yields (**3a–3p**) and moderate to good regioselectivity were obtained. Aryl ketones with electron-donating substituents were found to be effective directing groups, while electron-withdrawing substituents led to lower yields (**3a–3j**).[13] Heterocycle-containing ketones could be utilized (**3k** and **3l**), and a conjugated ketone was also tolerated (**3m**). Finally, alkyl-substituted ketones were suitable substrates, delivering the desired products in moderate to good yields (**3n–3p**). We then assessed the scope with respect to the alkenyl fragment of the substrate. Encouragingly, *γ,δ*-unsaturated and α-methyl ketones were viable substrates in 1,2-diarylation (**5a,b**).[14]

To showcase the versatility of this method, we subjected representative ketone product **1e** to a series of diversification reactions (Scheme 4). Classical functional group interconversions were performed to deliver a range of synthetically useful products (**6a–6e**). A Baeyer–Villiger oxidation reaction provided the corresponding aryl ester in good yield (**6a**). Alternatively, the ketone could be converted into an amide in a high-yielding Beckmann rearrangement (**6b**) or to a C=C bond through a Wittig olefination (**6c**). The ketone directing group would be re moved altogether with $LiAlH_4$ and $AlCl_3$ to afford **6d** in good yield, whilst reduction of the ketone to the corresponding secondary alcohol was obtained with $NaBH_4$ and took place in moderate yield, albeit with no diastereoselectivity (**6e**).

To gain insight into mechanistic aspects of this ketone-directed alkene 1,2-diarylation, we considered the binding mode of the directing group to the nickel catalyst. Under basic conditions, the substrate could in principle coordinate to the catalyst through the O-atom in either its ketone or enolate form (Scheme 5A).[7c] To probe this point, we first ran control experiments. Given that we observed isomerization of the starting materials to form the corresponding conjugated enones (such as **1a''**, see Table 1) under the reaction conditions, we questioned whether these byproducts were competent intermediates. In an enolate mechanism, conjugated enones could plau-

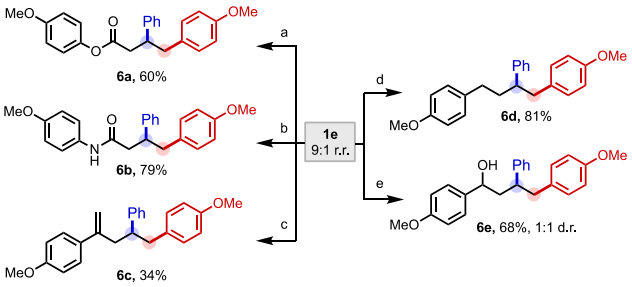
Scheme 3. Ketone and Alkene Scope.[a]



[a]Reactions performed on a 0.1 mmol scale. Percentages represent isolated yields. [b]Percentages represent ^{1}H NMR yields using CH_2Br_2 as internal standard.

sibly still participate in *β,γ*-diarylation through base-mediated

Scheme 4. Product Diversification.



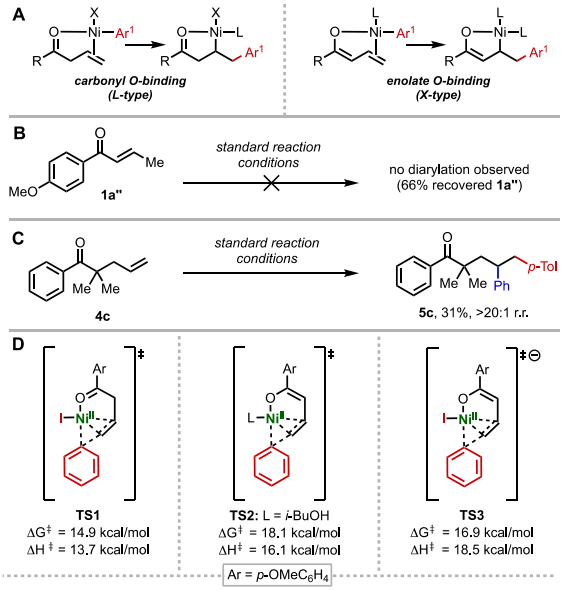
(a) *m*CPBA, TFA, anhydrous DCM, r.t. (b) H_2NOH•HCl, TFA, 70 °C. (c) Ph_3PCH_2Br, *n*-BuLi, THF, 70 °C. (d) $LiAlH_4$, $AlCl_3$, Et_2O/DCM, r.t. (e) $NaBH_4$, THF, reflux.

dienolate formation. In contrast, in the ketone mechanism, the conjugated enones would be dead ends. When we subjected independently prepared **1a''** to the reaction conditions, only unreacted starting material was observed (Scheme 5B). We next tested alkenyl ketone substrate **4c**, which lacks enolizable

protons; under standard conditions we isolated 31% yield of desired product **5c** (Scheme 5C). We attribute the low yield in this case to steric hindrance introduced by the *gem*-dimethyl group (for comparison see **5a**, Scheme 3).

Based on previous studies[3e] and Hammett data (see below), migratory insertion was identified as a likely candidate for the turnover-limiting step (for a depiction of the proposed catalytic cycle, see Scheme S10). Hence, to gain additional insight into

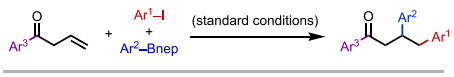
Scheme 5. Mechanistic Experiments.



the favored coordination mode, we compared plausible migratory insertion transitions states using density functional theory (DFT, see Scheme 5D). This analysis revealed that the neutral ketone form (**TS1**, $\Delta G^{\ddagger}$ = 14.9 kcal/mol) is lower in energy, in comparison to both the neutral enolate (**TS2**, $\Delta G^{\ddagger}$ = 18.1 kcal/mol) and anionic enolate forms (**TS3**, $\Delta G^{\ddagger}$ = 16.9 kcal/mol).[15,16] Collectively, the experimental and computational data are consistent with the carbonyl mechanism as the preferred pathway.

Finally, we investigated the effects of varying the electronic properties of the aryl iodide, arylboronate, and aryl ketone components on the reaction rate (see Scheme 6 and SI). Mirroring our previous findings using alkenyl amide substrates,[3e] we observed a negligible influence of ArB(nep) electronic properties on initial rate, whereas electron-neutral and -rich aryl iodides reacted faster than electron-poor electrophiles (ρ = 1.3). This trend points to a step involving the electrophile-derived aryl group as turnover-limiting, but is the opposite trend that

Scheme 6. Initial Rate Trends.



		p-OMe	*p*-Me	*p*-H	*p*-Cl	*p*-CF_3
	σ value	–0.27	–0.17	0.00	0.23	0.54
Ar^1–I	(v_{rel})	3.2	2.5	1.0	0.4	0.3
with Ph–B(nep) + *p*-OMePh‡						
Ar^2–B(nep)	(v_{rel})	0.7	1.6	1.0	1.0	0.8
with Ph–I + *p*-OMePh‡						
Ar^3‡	(v_{rel})	0.8	0.9	1.0	1.1	1.2
with Ph–I + Ph–B(nep)						

would be expected if oxidative addition were turnover-limiting. Hence, the data is consistent with migratory insertion as the turnover-limiting step. In terms of the aryl ketone electronic properties, we observed a moderately faster rate for electron-deficient aryl ketones, despite the fact that these substrates are ultimately low-yielding (ρ = 0.19). One potential explanation for this dichotomy is that electron-poor ketones succumb to off-cycle processes (e.g., isomerization) more easily, despite being inherently faster for the desired catalytic reaction. On the productive cycle, increased reaction rate with more electron-deficient carbonyl groups could reflect increased electronic activation of the alkene *via* inductive effects as shown in the ^{13}C resonances of the alkenyl carbon atoms across this series (see SI). An alternative explanation that cannot be ruled out at this time is that the carbonyl group partially dissociates during migratory insertion (and possibly re-coordinates subsequently to prevent β-H elimination).

In conclusion, we have demonstrated that a simple ketone can be used to direct nickel-catalyzed 1,2-diarylation of alkenes.[17] The products can be further manipulated using classical methods to yield a range of valuable building blocks. Mechanistic studies support a L-type carbonyl binding mode, while Hammett studies point to migratory insertion as the turnover-limiting step. We anticipate that the addition of ketones to the growing toolkit of native-directed 1,2-difunctionalization reactions will expand the utility of this suite of transformations.

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

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Detailed experimental procedures, compound characterization data, and copies of NMR spectra for new compounds (PDF) FAIR data file, including the primary NMR FID files, for compounds **1**, **1a**–**1z**, **2a**–**2p**, **3a**–**3p**, **5a**–**5c**, **6a**–**6e**, **S12**–**S13**.

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(11) One possible explanation for the modest effect of DMFU in the present system is that the isomerized starting material may act as an electron-deficient olefin ligand, making the added DMFU somewhat redundant. This hypothesis is supported by DFT (see SI) and by the observation that γ,δ-unsaturated ketone substrate (**4a** → **5a**) is low-yielding in the absence of DMFU (9% yield, see SI).

(12) Minimal isomerization is observed for the majority of examples (≤10%), and there is no clear relationship between the amount of isomerized byproduct and the yield of the desired product.

(13) With the *para*-Cl and -CF_3 aryl ketones, uncharacterized side products were formed, complicating separation. ^{1}H NMR yields are reported to illustrate reactivity trends across the entire electronic series.

(14) For **(±)-5b,** PhI and PhB(nep) were used to simplify analysis to avoid formation of regioisomers as well as diastereomers.

(15) **TS4** and **TS5** with L = DMFU and L = COD, respectively, were computed to be higher in energy than **TS2**. See the SI for details.

(16) Using d_4-methanol under otherwise standard conditions, 19% deuterium incorporation at the α-position was observed in the product. This result is inconsistent with an enolate pathway since ≥50% deuterium incorporation would be expected in this case (see SI).

(17) A previous version of this paper was deposited on a preprint

server: Kleinmans, R.; Apolinar, O.; Derosa, J.; Karunananda, M. K.; Li, Z.-Q.; Tran, V. T.; Wisniewski, S. R.; Engle, K. M. Nickel-Catalyzed 1,2-Diarylation of Alkenyl Ketones: A Comparative Study of Carbonyl-Directed Reaction Systems, *ChemRxiv* **2021**, DOI: 10.26434/chemrxiv.14150174.