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Multimetallic Ni- and Pd-Catalyzed Cross-Electrophile Coupling To Form Highly Substituted 1,3-Dienes

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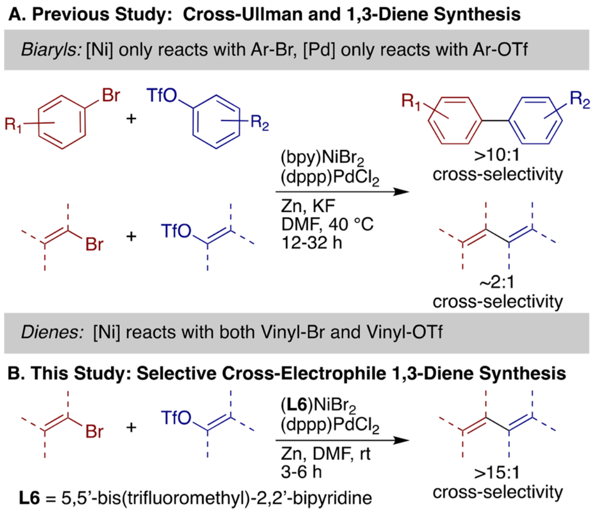
Supporting Information

ABSTRACT: The synthesis of highly substituted 1,3-dienes from the coupling of vinyl bromides with vinyl triflates is reported for the first time. The coupling is catalyzed by a combination of (5,5′-bis(trifluoromethyl)-2,2′-bipyridine)$NiBr_2$ and (1,3-bis(diphenylphosphino)-propane)$PdCl_2$ in the presence of a zinc reductant. This method affords tetra- and penta-substituted 1,3-dienes that would otherwise be difficult to access and tolerates electron-rich and -poor substituents, heterocycles, an aryl bromide, and a pinacol boronate ester. Mechanistically, the reaction appears to proceed by an unusual zinc-mediated transfer of a vinyl group between the nickel and palladium centers.

The 1,3-diene is an important synthetic target because it participates in an increasing variety of useful transformations, including hydrofunctionalizations, ring-forming reactions, and polymerizations. The diene also occurs in many natural products with interesting biological activity.[1] A natural disconnection for the 1,3-diene motif is the formation of the central single bond. For linear and less-substituted branched dienes, Mizoroki-Heck,[2] ene-yne metathesis,[3] C−H vinylation,[4] and cross-coupling approaches[5] have been successful. For highly substituted and branched dienes with multiple rings, the most-used approach is cross-coupling of vinylmetal reagents with vinyl halides.[1,6] Though these approaches have proven useful, relatively few highly substituted dienes have been synthesized and often require synthesis of an organometallic reagent.

An alternative strategy to synthesize highly substituted 1,3-dienes would be the cross-electrophile coupling of two cyclic vinyl electrophiles, but no general approach of this type has been reported. We recently reported a cross-Ullman strategy toward biaryls that relied on complementary reactivity of nickel[7] and palladium toward aryl bromides and aryl triflates, but the selectivity was poor for vinyl bromides with vinyl triflates and the scope was limited (Scheme 1A).[8,9] We hypothesized that this was due to the fact that the nickel catalyst was poorly selective for vinyl bromides over vinyl triflates,[10] but it was not clear if the nickel and palladium catalyst system could be applied to these more reactive substrates. Furthermore, the mechanism of the reaction was poorly understood, limiting development. Overcoming these challenges would be useful in synthesis: the stoichiometric version of this coupling was recently used at a late stage in an approach to Batrachotoxin.[11] Herein, we report a new nickel catalyst that allows for the selective cross-coupling of vinyl bromides with vinyl triflates without an excess of either coupling partner (Scheme 1B) as well as insight into the dual role of zinc in the process.

Scheme 1. Cross-Electrophile 1,3-Diene Synthesis



We began our studies by testing the coupling of vinyl bromide **1a** with vinyl triflate **2a** under catalysis by nickel and palladium with a variety of ligands and examined the distribution of products between the cross-coupled product **3a** and the homocoupled vinyl bromide **5** and the homocoupled vinyl triflate **4**. These studies, summarized in Table 1, showed that the nitrogen ligand has a large influence on selectivity whereas the phosphorus ligand does not (see Supporting Information, Chart S2).[12] Tridentate and hindered bidentate ligands were selective for homodimer formation (**L10**−**L12**), but a variety of bidentate bipyridine and phenanthroline ligands provided promising results. Among these ligands, bipyridine **L6**, containing electron-withdrawing trifluoromethyl groups, provided the best balance of selectivity and reactivity.[13] Bipyrimidines **L7** and **L8** were selective, but reactions did not proceed to completion. More electron-rich ligands (**L3** and **L4**) were both poorly selective and slow. These results are in stark contrast to our results on biaryl synthesis,[8] where the phosphine was crucial and the nitrogen ligand was relatively unimportant, demonstrating the adaptability of this new system.

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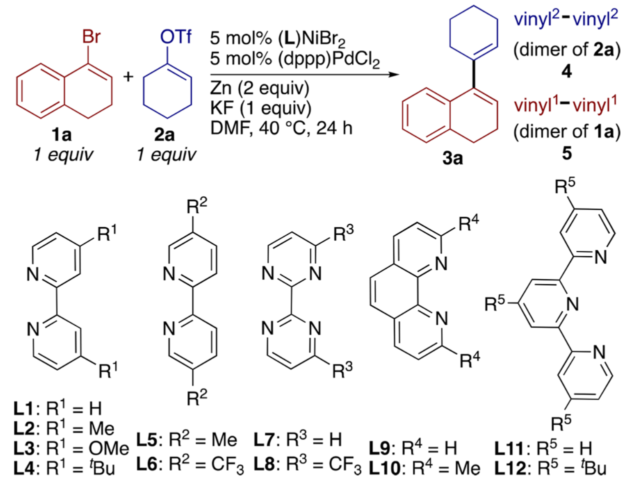
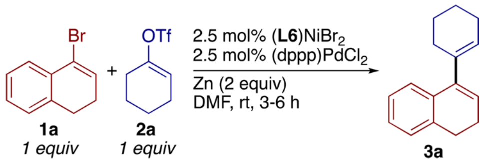
Table 1. Nitrogen Ligand Effect on Diene Synthesis[a]



entry	L	3a (%)[b]	4 (%)[b]	5 (%)[b]	3a:4 (3a:5)
1	**L1**	70	31	16	2.3 (4.4)
2[c]	**L2**	37	9	16	4.1 (2.3)
3[c]	**L3**	28	16	0	1.8 (NA)
4[c]	**L4**	18	15	0	1.2 (NA)
5[c]	**L5**	53	26	5	2.0 (13)
6[d]	**L6**	82	14	9	5.9 (9.1)
7[c]	**L7**	62	9	3	6.9 (21)
8[c]	**L8**	26	6	1	4.3 (26)
9[c]	**L9**	9	2	0	4.5 (NA)
10[c]	**L10**	8	20	0	0.4 (NA)
11	**L11**	43	73	50	0.6 (0.9)
12	**L12**	38	60	34	0.6 (1.1)

[a]Reactions were run on 0.5 mmol scale in 2 mL of solvent. Byproduct **4** corresponds to the dimer of **2a**; byproduct **5** corresponds to the dimer of **1a**. dppp = 1,3-bis(diphenylphosphino)propane. [b]Yields are corrected GC yields vs dodecane as internal standard. [c]Both starting materials remained after 24 h. [d]Reaction complete in 3 h.

Table 2. Optimization of Reaction Conditions[a]



entry	change in conditions	3a (%)[b]	3a:4 (3a:5)
1	KF (1 equiv), 5 mol % catalysts	95	19 (32)
2	5 mol % catalysts	94	18 (31)
3	none	95/89[c]	19 (32)
4	40 °C	94	16 (19)
5	60 °C	84	7.0 (8.4)
6	80 °C	79	5.3 (4.2)
7[d]	1.25 mol % catalysts	97	19 (32)
8	no (dppp)PdCl$_2$	59	3.1 (3.5)
9[e]	no **L6**	0	NA
10	no dppp	83	7.5 (6.4)
11[e]	no Ni	0	NA
12[e]	no Zn	0	NA
13	under N$_2$ on bench	94	25 (47)
14	under air on bench	76	5.2 (31)

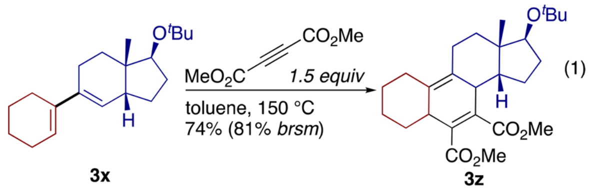
[a]Reactions were run on 0.5 mmol scale in 2 mL of solvent. [b]Yields are corrected GC yields vs dodecane as internal standard. Balance of yield was dimeric products unless otherwise noted. [c]Isolated yield after purification. [d]Reaction complete after 24 h. [e]Starting materials were not consumed.

Examining the other reaction parameters also led to further improvements in conditions (Table 2). Higher temperatures led to lower selectivity (entries 3–6), but lower catalyst loading did not alter the yield dramatically (entries 2, 3 and 7). Finally, reactions set up on the bench under N$_2$ (entry 13), or even under air (entry 14), provided good yields of product.

Control reactions showed that the addition of KF did not have an effect on yield or selectivity (entries 1–2). This result again is in sharp contrast to our previous biaryl study,[8] where potassium fluoride was crucial to high selectivity, presumably by improving the selectivity of the palladium catalyst for aryl triflate over aryl bromide.[14] This suggests different factors are crucial to selectivity in this system. Though no product was formed in the absence of **L6**, Ni, or Zn, significant product was formed in the absence of dppp (entry 10) or even (dppp)PdCl$_2$ (entry 8). The lower selectivities in these reactions suggest that both nickel and palladium are essential for high cross-product selectivity, but not for product formation.

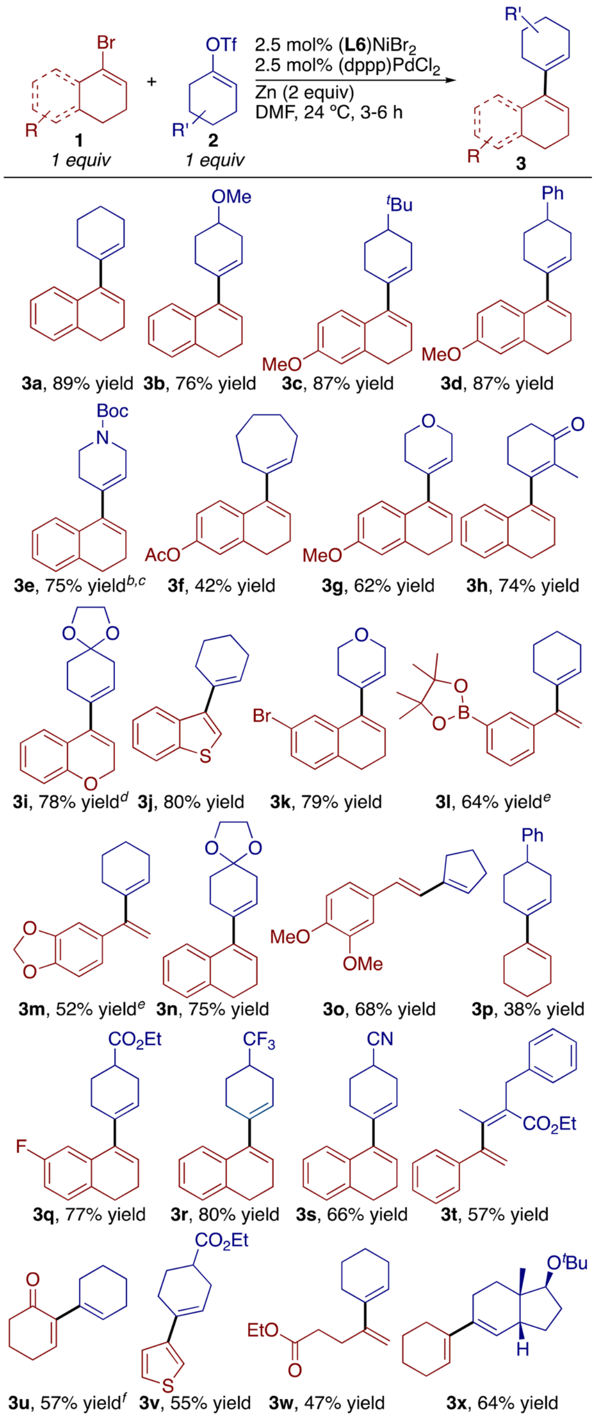
These conditions proved to be general for a variety of cycloalkenyl as well as several acyclic alkenyl electrophiles (**3m**, **3o**, **3t**, **3w**) (Table 3). Thiophene (**3v**) and benzothiophene (**3j**) could also be selectively coupled with vinyl triflates, but these conditions were unselective for the coupling of aryl bromides with aryl triflates.[8,15] A variety of functional groups were tolerated, including protected nitrogen (**3e**), enone (**3h**, **3u**), boronic acid ester (**3l**), nitrile (**3s**), and even an aryl bromide (**3k**). Although substrates with little steric or electronic differentiation provided lower selectivity (**3p**), even small differences in sterics or electronics could allow for reasonable selectivity (**3x**). Finally, the yield of **3v** was the same on bench at a 5.0 mmol scale as in the glovebox at a 1.0 mmol scale (see Supporting Information).

Most of the dienes synthesized in Table 3 would be difficult or impossible to form by Heck or metathesis approaches because of their substitution patterns. The difficulty in accessing these types of dienes is reflected by the fact that only one example (**3u**) in Table 3 has been previously reported. Compared to other cross-coupling approaches,[6] the direct use of two different electrophiles can save steps and improve functional-group compatibility. For example, dienes like **3x** (Table 3) have been previously synthesized by a Stille-coupling strategy,[16] but our approach avoids the need to synthesize a vinyltin reagent. These dienes can participate in a variety of pericyclic reactions to form steroid analogs (e.g., **3z** in eq 1 and Supporting Information).



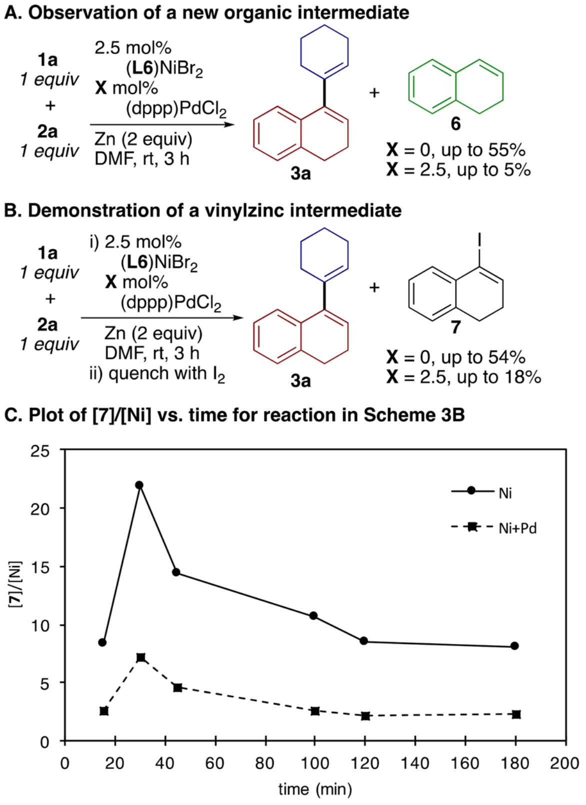
A key mechanistic question for this multimetallic reaction is how vinyl groups are transferred between metal centers. Though direct nickel–palladium transmetalation has been proposed,[8] little evidence has been reported. In order to better understand the roles of the two catalysts in these reactions, we decided to study reactions catalyzed by nickel alone as well as reactions catalyzed by a combination of nickel and palladium. Monitoring reaction progress under both conditions provided an important

Table 3. Scope of Cross-Coupling Reaction[a]



[a] Reactions were run on 1.0 mmol scale in 4 mL of DMF. Yields of isolated, purified material. See Supporting Information. [b] BINAP was used instead of dppp. [c] Yield of **3e** was adjusted to account for 8.6 wt % of inseparable *tert*-butyl 3,6-dihydropyridine-1(2*H*)-carboxylate. [d] Yield of **3i** was adjusted to account for 4.7 wt % of inseparable [1,1′-bi(cyclohexane)]-1,1′diene. [e] 1.5 equiv of vinyl bromide used. [f] 2-Chlorocyclohex-2-en-1-one was used.

Scheme 2. Evidence for a Vinylzinc Intermediate[a]


A. Observation of a new organic intermediate

B. Demonstration of a vinylzinc intermediate

C. Plot of [7]/[Ni] vs. time for reaction in Scheme 3B

[a] See Supporting Information for additional information. The intermediates were quantitated by GC, corrected.

observation: aliquots quenched with acid contained 1,2-dihydronaphthalene (**6**, Scheme 2A) and aliquots quenched with I_2[17] contained 1-iodo-1,2-dihydronaphthalene (**7**, Scheme 2B). Both **6** and **7** could be formed from reaction of either a vinylnickel or vinylzinc reagent. However, although the concentration of **6** and **7** that built up during the first 30 min of reactions was small, it exceeded the nickel loading ($[7]/[\mathrm{Ni}] > 1$) and decreased with time (Scheme 2C and additional experiments in the Supporting Information). This suggests that both **6** and **7** are derived from quenching of the same vinylzinc intermediate and not from quenching of a vinylnickel intermediate.[18]

These results are most consistent[19] with zinc-mediated transfer of the vinyl group of **1a** from nickel to palladium[20] via a transient vinylzinc intermediate[21,22] and subsequent palladium-catalyzed C−C bond formation.[1] Though the use of organozinc intermediates in cross-coupling is well-known, and in situ organozinc synthesis and coupling has been reported,[23,24] the zinc mediated transfer of groups between two different catalysts has not been exploited in small molecule synthesis. In polymer chemistry, however, this strategy has been used in chain shuttling copolymerization, where a zinc-*co*-catalyst transfers growing polymer chains between two different catalysts.[25] This important concept in polymer chemistry could also have wide application in small molecule synthesis. Further mechanistic studies are ongoing.

In conclusion, we have developed a general reductive approach to highly substituted 1,3-dienes that tolerates a wide array of functionality. This approach demonstrates that the nickel and palladium system can be tuned to selectively couple two highly reactive electrophiles. Furthermore, the zinc-mediated transfer of organic moieties between two catalysts has not been extensively explored and could provide a new general mechanism for cross-coupling.

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b13601.

Optimization data, mechanistic experiments, detailed experimental procedures, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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(12) Several phosphine ligands proved to be effective, including **L13** and **L14**. We chose to keep **L19** as the phosphine ligand for this system because further experiments demonstrated that **L19** and **L14** worked equally well (see Supporting Information, Chart S4).

(13) Our ranking of the relative donicity of a subset of these ligands: **L6** < **L7** < **L1** < **L4** < **L3**. We ranked the ligands using an adaptation of Girolami's DFT method: Flener Lovitt, C.; Frenking, G.; Girolami, G. S. *Organometallics* **2012**, *31*, 4122 The absolute values and range of values for the calculated νCO are very close to those calculated by Girolami for dppe derivatives substituted with aryl and alkyl substituents.

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(15) These conditions give poor cross-selectivity for biaryl syntheses in reference 8. Applying the conditions from Table 3 to the coupling of bromobenzene with 4-anisyl triflate resulted in a 47% isolated yield of cross-product, 4-methoxy-1,1′-biphenyl. The remaining mass balance consisted of homodimers of the starting materials.

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(18) We cannot rule out the possibility that a small portion of the **6** and **7** observed are derived from reaction of vinylnickel(II) intermediates with acid and I_2. In Scheme 2C, this could account for a maximum [**7**]/Ni of 2. We observed only trace 1-iodocyclohexene, suggesting that a vinylzinc species derived from **2a** is not important.

(19) The possibility that **6** could be converted to product by a Heck reaction was ruled out by studying the reactivity of **6** with **2a** under catalytic conditions. See Supporting Information, page S35.

(20) A small amount of direct nickel-palladium transmetalation cannot be ruled out. At this time, it is not clear if zinc mediated transfer occurs in reactions with aryl bromides. The vinylzinc is not formed by direct insertion, see Table 1, entry 11.

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