A Palladium-Catalyzed Three-Component-Coupling Strategy for the Differential Vicinal Diarylation of Terminal 1,3-Dienes

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Supporting Information

ABSTRACT: A palladium-catalyzed intermolecular vicinal diarylation of terminal 1,3-dienes using aryldiazonium tetrafluoroborates and arylboronic acids is reported. Using this technology, two different arenes are regioselectively introduced in a vicinal fashion across the terminal alkene of a variety of terminal 1,3-dienes at ambient temperature. Through the action of a chiral bicyclo[2.2.2]octadienyl ligand at −20 °C, good enantioselectivity has also been achieved.

A number of intermolecular alkene diarylation reactions have been developed wherein 2 equiv of a single arene are added to an alkene in a single step. Consequently, two identical aryl groups are incorporated. In the interest of rapidly generating complexity from simple feedstock starting materials, there is a strong desire to develop single-step alkene diarylation reactions wherein different arenes are added across an alkene selectively in the presence of a palladium catalyst. While norbornadiene, terminal allenes, and more recently simple terminal alkenes have been used as substrates in three-component diarylations, selective three-component diarylations of terminal 1,3-dienes are not yet known. Three-component couplings of terminal 1,3-diene substrates attracted our interest because, unlike the aforementioned technologies, we envisioned that the products could retain an alkene functional group and also incorporate a chiral center.

Our approach to the vicinal difunctionalization of terminal 1,3-dienes is shown in Scheme 1A. Mechanistically, such reactions are initiated upon oxidative addition of an sp² carbon electrophile to Pd(0). This generates a cationic Pd-alkyl species that may undergo migratory insertion and defer transmetalation if the leaving group is noncoordinating (Scheme 1B). The resultant Pd-alkyl is stabilized as a π-allyl that resists β-hydride elimination. To complete the difunctionalization sequence, transmetalation and reductive elimination of the second sp² coupling partner, R₂, affords the product E. This strategy was implicated in our previous vicinal alkenyarylation of 1,3-dienes, which gave products of the type F (Scheme 1C). Unfortunately, our attempts to develop an analogous three-component diarylation by using aryl triflates instead of alkanyl triflates consistently failed, which is likely a result of the relative inertia of aryl triflates. We now wish to report the successful development of a three-component vicinal diarylation of 1,3-dienes, which employs aryldiazonium tetrafluoroborates and aryl boronic acids as coupling partners, affording products of type G (Scheme 1D). We have also identified a chiral bicyclo[2.2.2]octadienyl ligand that is capable of delivering diarylation products with good levels of enantioselective enrichment.

We began the study by optimizing the coupling of trans-1-(para-methoxyphenyl)-1,3-butadiene 1a with phenyldiazonium tetrafluoroborate and phenylboronic acid (Table 1). Aryldiazonium tetrafluoroborates were chosen not only because they readily oxidize Pd(0) but also because they afford the aforementioned requisite cationic aryl-Pd intermediates required for migratory insertion (see A in Scheme 1B). Starting with our previously reported alkenyarylation conditions, the indicated Heck product predominated over both the desired vicinal diarylation product 2a and the Suzuki product (entry 1).

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In contrast to N,N-dimethylacetamide (DMA), 1,4-dioxane minimized Heck product formation but afforded an equimolar ratio of 2a and the Suzuki product (entry 2). Interestingly, another ethereal solvent, THF, afforded only trace amounts of 2a and an equimolar ratio of Suzuki and Heck products (entry 3). Next, alcoholic solvents, which have proven valuable in differential geminal diarylations of terminal alkenes with diazonium salts and boronic acids, were examined. While trace amounts of 2a and mostly the Heck product were observed in methanol (entry 4), increasingly bulky alcohols led to improved yields of 2a at the expense of the Heck product (entries 4–8). In particular, the use of tert-amyl alcohol afforded superior selectivity for the desired diarylation product over both Heck and Suzuki products (entry 8). Comparable results were obtained when the reaction was carried out at ambient temperature (entry 9) and with NaHCO3 in place of KF (entry 10). The final breakthrough was the addition of exogenous dibenzylideneacetone (dba), which improved the yield significantly, presumably by preventing the detrimental accrual of unligated Pd(0) (entry 11).9,10

Under the optimized conditions, we initially investigated increasingly electron-deficient trans-1-phenyl-1,3-butadienes 1b and 1c in order to directly compare 1-aryl-1,3-diene electronic effects on vicinal diarylations (Figure 1). These substrates afforded diminishing yields of the corresponding 1,3,4-triaryl-1-butene products 2b (65%) and 2c (52%), although the selectivity for the difunctionalization product remained >95% in these cases and all subsequent ones. Next, trans-1-(para-fluorophenyl)-1,3-butadiene 1d was found to react efficiently with para-methoxyphenyldiazonium tetrafluoroborate and phenylboronic acid, affording an 83% yield of 2d. Additionally, the reaction between (E)-1-(1-naphthyl)-1,3-butadiene, 4-nitrophenyldiazonium tetrafluoroborate, and phenyl boronic acid delivered the designated nitrophenyl-containing product 2e in 50% yield.

Having established the broad tolerance of electronically disparate terminal 1,3-dienes and phenyldiazonium salts in 2a–

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**Table 1. Optimization of the Three-Component-Coupling of 1a with Phenyl Diazonium Tetrafluoroborate and Phenyl Boronic Acid**

| entry | base | solvent  | conv (%)a of 1a | yield (%)a of 2a | selectivitya (2a/Suzuki/Heck) |
|-------|------|----------|----------------|----------------|-----------------------------|
| 1     | KF   | DMA      | 70             | 8              | 04:04:92                   |
| 2     | KF   | 1,4-dioxane | 100            | 14             | 50:50:tr                  |
| 3     | KF   | THF      | 100            | tr             | 50:50                      |
| 4     | KF   | MeOH     | 100            | tr             | 05:19:76                  |
| 5     | KF   | EtOH     | 100            | 4              | 14:14:72                  |
| 6     | KF   | i-PrOH   | 100            | 11             | 62:13:25                  |
| 7     | KF   | t-BuOH   | 100            | 33             | 92:02:06                  |
| 8     | KF   | t-AmylOH | 93             | 53             | 94:03:03                  |
| 9     | KF   | t-AmylOH | 90             | 57             | 96:02:02                  |
| 10b   | NaHCO3 | t-AmylOH | 96             | 58             | 94:04:02                  |
| 11b,c | NaHCO3 | t-AmylOH | 100            | 80             | 94:04:02                  |

“Determined by GC analysis using dodecane as an internal standard following response factor correction.” This reaction was conducted at room temperature. “An additional 15 mol % of dba was added to this reaction.”

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**Figure 1.** Exploration of the scope of coupling partners in the three-component diarylation of terminal 1,3-butadienes. The isolated yield of each product is reported.
 Arylpropionic acids, and their asymmetric synthesis has not been achieved. Thus, a catalytic asymmetric route starting with N-aryl allylic alcohols would streamline the access to enantioenriched variants of the phenyl group. From terminal 1,3-dienes, which are prepared in one step, would afford 1,3,4-triphenyl-1-butene in just 3% enantiomeric excess (Table 2, entry 1). A substantial improvement was observed through the use of bicyclo[2.2.2]octadienyl ligand L2, which afforded 2b in 29% ee (entry 2). Focusing on the bicyclo[2.2.2]octadienyl core, we found that the pseudo C2-symmetric (R)-(−)-carvone-derived ligand L3 delivered 2b in 51% ee (entry 3), while (R)-(−)-α-phellandrene-derived L4 performed the best under these conditions, affording a promising 65% ee (entry 4). A brief temperature profile revealed that the enantioselectivity could be improved by decreasing the temperature, albeit at the expense of the reaction yield. At −8 °C, just above the freezing point of tert-AmyLOH, 83% ee was observed, albeit with a low 10% yield of 2b (entry 5). Conversely, increasing the temperature to 40 °C resulted in an improved yield (51%) but a diminished ee (55%, entry 7).

Our final aim was to improve the yield of the asymmetric diphenylation using L4 while preserving enantiomeric excesses. To this end, 1,2-dichloroethane (DCE) was selected as the solvent, enabling the reaction to be carried out at −20 °C, while a slight excess of 1,3-diene substrates and increases in catalyst, ligand, and base loading were also employed (Figure 2). Under these conditions, terminal dienes 1a−1c could be converted to the corresponding (R) enantiomers in 75−82% ee and in isolated yields of 25−30%. Neither the yield nor the selectivity was found to depend significantly on the electronic nature of the diene, with electron-rich (1a), electron-neutral (1b), and electron-deficient (1c) substrates behaving similarly. This asymmetric variant resisted our best efforts to increase the yield by changing the conditions or the technical procedure.

In summary, we have developed a highly regioselective vicinal diarylation reaction of terminal 1,3-dienes that incorporates two different aryl groups from diazonium salts and boronic acids. The reaction is conducted under mild conditions, incorporates a variety of functionalized arenes, and can be rendered enantioselective through the use of a chiral bicyclo[2.2.2]octadienyl ligand, albeit in low yield. New

| Table 2. Selected Ligand and Temperature Effects on Asymmetric Induction in the Vicinal Diphenylation of (E).1-Phenyl-1,3-butadiene |
|---|---|---|---|
| entry | temp. (°C) | ligand | yield (%) | ee (%) |
| 1 | L1 | n.d. | 3 |
| 2 | L2 | n.d. | 29 |
| 3 | L3 | n.d. | 51 |
| 4 | L4 | n.d. | 65 |
| 5 | L5 | 40 | 83 |
| 6 | L6 | 40 | 33 |
| 7 | L7 | 40 | 51 |

* Determined by GC analysis using dodecane as an internal standard following response factor correction. b Determined by SFC analysis.
approaches to asymmetric three-component-coupling reactions are currently under investigation.

ASSOCIATED CONTENT
4 Supporting Information

Experimental procedures, full spectroscopic data for new compounds, and chiral separations. 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 interest.

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