Rapid access to unsymmetrical tolanes and alkynones by sequentially palladium-catalyzed one-pot processes†‡

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Alkynones as well as unsymmetrically substituted tolanes (diarylalkynes) can be rapidly generated in a one-pot fashion via sequential palladium catalysis. Terminal alkynes, formed in situ by protecting-group free palladium-catalyzed coupling of aryl iodides with ethynyl magnesium bromide, are subsequently transformed by Sonogashira coupling with aryl halides or aryl halides to furnish unsymmetrically substituted alkynes in good to excellent yields.

Unsymmetrically substituted alkynes are valuable building blocks in heterocycle synthesis and, in their own right, exhibit interesting properties for applications in molecular electronics. The most common approach to this class of molecules is the palladium-catalyzed coupling of aryl halides or aryl halides with terminal alkynes, which are usually synthesized by Sonogashira coupling of a second aryl halide with trimethylsilyl acetylene (TMS acetylene), followed by work up, isolation, and desilylation. While several one-pot approaches to unsymmetrically substituted tolanes, i.e. diarylalkynes, are known, protected acetylene species such as TMS acetylene, propiolic acid, or methyl butynol are usually applied, followed by in situ deprotection and coupling. No analogous one-pot synthesis of alkynone derivatives has so far been published to the best of our knowledge. We herein present a protecting-group free, sequentially palladium-catalyzed multicomponent approach towards alkynones and unsymmetrically substituted tolanes in a one-pot fashion.

In the conception of this novel one-pot approach we first reasoned that intermediate terminal alkynes can be generated in situ by a palladium-catalyzed Kumada-type coupling of aryl iodides with ethynyl magnesium bromide originally presented by Negishi and coworkers. Ethynyl magnesium bromide is a commercially available activated acetylene species and can be considered as the precursor of the commonly employed TMS acetylene. Most advantageously, the reagent is easy to handle and the only side product is the corresponding magnesium halide. Therefore, a subsequent Sonogashira coupling could be concatenated in a one-pot fashion with no further addition of palladium catalyst.

Table 1 Sequentially Pd-catalyzed three-component synthesis of alkynones 4 from aryl iodides 1, ethynyl magnesium bromide (2), and aryl chlorides 3

| Entry | Product | Aryl 1 | Aryl 2 | Yield of alkynone 4 (%) |
|-------|---------|--------|--------|-------------------------|
| 1     | 4a      | 4-MeOC6H4 | Ph     | 81                      |
| 2     | 4b      | 4-MeOC6H4 | 4-Tol  | 80                      |
| 3     | 4c      | 3,4,5-(MeO)C6H3 | Ph     | 68                      |
| 4     | 4d      | 3,4,5-(MeO)C6H3 | 2-Thienyl | 76                      |
| 5     | 4e      | Ph      | Ph     | 86                      |
| 6     | 4f      | 4-Me2NC6H4 | Ph     | 79                      |
| 7     | 4g      | 2-Naphthyl | Ph     | 82                      |
| 8     | 4h      | 4-Me2NC6H4 | 4-FCC6H4 | 60                      |
| 9     | 4i      | 4-Me2NC6H4 | 4-NCC6H4 | 74                      |
| 10    | 4j      | Ph      | 4-MeOC6H4 | 59                      |

Scheme 1 Pseudo-five component synthesis of 3,3’-(1,4-phenylenebis(1-phenylprop-2-yn-1-one)) (4k) from 1,4-diiodobenzene (1a), ethynyl magnesium bromide (2), and benzoxyt chloride (3a).
Indeed, this sequentially Pd-catalyzed reaction can be performed within 2 h by first reacting aryl iodides with ethynyl magnesium bromide under modified Kumada conditions, followed by partial neutralization with substoichiometric amounts of triethylammonium chloride and coupling with aryl chlorides in the presence of catalytic amounts of CuI and a stoichiometric amount of triethylamine, followed by aqueous work up and simple flash chromatography. The Kumada-type alkylation was originally performed by Negishi et al. using tetrakis(triphenylphosphane)palladium(0). This catalyst, however, gave only traces of alkynone in the subsequent Sonogashira coupling with aryl chlorides. Changing the palladium species to bis(triphenylphosphane)palladium(0) dichloride required a slightly higher temperature for the initial alkylation but gave good yields in the concluding alkynone formation. As a result, 10 alkynones were obtained in good to very good yields (Table 1).

A quick access is also offered to push–pull substituted derivatives \( i \) and \( j \), thus establishing a quick entry to heterocycles with interesting photophysical properties. By employing 1,4-diiodobenzene (1a) as aryl iodide component, bisalkynyl derivative 4k can be easily accessed (Scheme 1).

Employing a second aryl halide 5 in the Sonogashira coupling gives access to diarylalkynes (Table 2). The Sonogashira coupling with aryl iodides \( a \)–\( f \) proceeds at room temperature within 1.5 h. Activated aryl bromide 5g bearing a cyano group can also be employed by using slightly elevated temperature and prolonged reaction time. Eight diarylalkynes were synthesized by this one-pot sequence in good to excellent yields (Table 2). Upon using Pd(PPh3)4 as a Pd source, lower yields of product 6a (64%) were obtained in comparison to Pd(PPh3)4Cl2 as a catalyst, which gave compound 6a in 81% yield (Table 2, entry 1).

By employing \( p \)- and \( m \)-diiodobenzene 1a and 1b as starting materials, the corresponding bis(arylethynyl)benzene derivatives 2i and 2j are easily accessible (Scheme 2) via a pseudo-five component reaction with a respective yield of 91% and 97% per bond formation. These types of conjugated oligo(phenylenethynlenes) are of potential interest as molecular wires or in the preparation of cruciform fluorophores.

In addition, arylethynyl phenothiazine derivatives 2k and 2l can be readily prepared. These compounds have aroused particular interest for the corrosion protection of metal surfaces. It is noteworthy to mention that the previous multi-step approach required several days for performing the concluding Sonogashira coupling. By using the Kumada–Sonogashira methodology, the overall reaction time can be shortened to two hours starting from 10-hexyl-3-iodo-10H-phenothiazine (Scheme 3).

Finally, an addition extension of the methodology to three Pd-catalyzed steps in a one-pot fashion is also possible. When

### Table 2 Sequentially Pd-catalyzed three-component synthesis of diarylalkynes from aryl iodides, ethynyl magnesium bromide, and aryl halides

| Entry | Product | Aryl1 | Aryl2 | X | Yield of diarylkyne 6 (%) |
|-------|---------|-------|-------|---|-------------------------|
| 1     | 6a      | 4-MeOC6H4 | 4-CIC6H4 | I | 81                      |
| 2     | 6b      | 4-MeOC6H4 | 4-BrC6H4 | I | 86                      |
| 3     | 6c      | 4-MeOC6H4 | Ph      | I | 78                      |
| 4     | 6d      | Ph      | 4-Pyridyl | I | 80                      |
| 5     | 6e      | 4-NC6H4  | 4-FC6H4 | I | 83                      |
| 6     | 6f      | 4-FC6H4  | 1-Naphthyl | I | 65                      |
| 7     | 6g      | 4-CIC6H4 | Ph      | I | 67                      |
| 8     | 6h      | 4-MeOC6H4 | 4-NCC6H4 | Br | 64                      |

### Scheme 2 Pseudo-five component synthesis of bis(arylethynyl)benzene compounds 6i and 6j.

### Scheme 3 Synthesis of arylethynyl phenothiazine derivatives 6k and 6l.

### Scheme 4 Four-component synthesis of 4’-((4-methoxyphenylethynyl)-[1,1’-biphenyl]-4-carbonitride (8) by a sequentially Pd-catalyzed Kumada–Sonogashira–Suzuki process.
4-bromo-1-iodobenzene (1c) is employed in the second step, the carbon–bromine bond becomes available for a concluding Pd-catalyzed Suzuki coupling with 4-cyanophenylpinacolboronic ester (7), furnishing biaryl-substituted alkyne 8 in moderate yield (Scheme 4) in the sense of a sequentially catalyzed four-component Kumada–Sonogashira–Suzuki process with 77% yield per coupling. The conditions for the terminal Suzuki coupling step were adapted from related Sonogashira–cylocondensation–Suzuki sequences.14

Conclusions

In summary, we have disclosed a convenient and versatile sequentially palladium-catalyzed synthesis of unsymmetrically substituted alkynes. The modular nature of the process, the readily available starting materials, the omission of protecting groups for the ethynyl arene formation, the mild reaction conditions, and the short reaction times open a quick and straightforward access to a large variety of disubstituted alkynes. The mild reaction conditions for the ethynyl arene formation, the mild reaction conditions, and the short reaction times open a quick and straightforward access to a large variety of disubstituted alkynes in a one-pot fashion. Moreover, the palladium catalyst is employed in a sequential fashion, catalyzing two or even three different subsequent cross-coupling reactions without any further addition. The extension of the reaction sequence to one-pot syntheses of heterocycles and further sequences is currently underway.

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