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Pd-Catalyzed α-Arylation of Nitriles and Esters and γ-Arylation of Unsaturated Nitriles with TMPZnCl·LiCl

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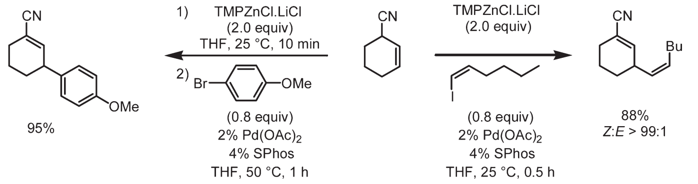
ABSTRACT



Using TMPZnCl·LiCl as a kinetically highly active base, nitriles and esters undergo a Pd-catalyzed α-arylation under mild conditions. Remarkably, in the case of α,β- or β,γ-unsaturated nitriles, a regioselective γ-arylation or a γ-alkenylation is observed.

The Pd-catalyzed arylation of carbonyl derivatives and related functional groups has significantly extended the scope of enolate chemistry.[1] Several bases have been used to generate α-metalated nitriles and carbonyl derivatives. These metal enolates produce, after reductive elimination of an intermediate arylpalladium(II), various α-arylated carbonyl compounds.[2−5] Hagadorn has reported the use of TMP$_2$Zn to deprotonate amides and esters. He

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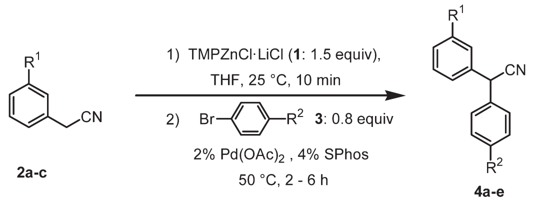
performed Pd-catalyzed cross-couplings using Pd_2dba_3 and $t Bu_3P$ as catalytic system.[6] The choice of the appropriate base, the palladium catalyst, and the reaction conditions is essential for obtaining high yields. Recently, Hartwig reported silyl ketene acetals as enolate equivalents in a new Pd-catalyzed γ-arylation of α,β-unsaturated esters.[7] In an alternative approach, Baudoin developed a direct β-arylation of carbonyl compounds through an α-metalation–elimination–addition sequence.[8]

We developed a range of LiCl-solubilized TMP-bases[9] (TMP = 2,2,6,6-tetramethylpiperidyl) which directly generate functionalized organometallics ideally suited for transition metal coupling. The bases are monomeric in solution, bear a sterically hindered TMP-moiety coordinated to LiCl, and display an exceptionally high kinetic basicity. Contrary to less hindered amines such as $i Pr_2NH$ or $(Me_3Si)_2NH$, TMPH does not slow down Pd-catalyzed Negishi cross-couplings.[10] These bases are excellent for deprotonating various functionalized aromatics and heteroaromatics. We envisioned using some of these TMP-bases to generate metal enolates directly to improve subsequent transition metal couplings. Herein, we report the use of TMPZnCl·LiCl[8e-h] (**1**) for the Pd-catalyzed α-arylation of nitriles and esters as well as a new γ-arylation and γ-alkenylation of unsaturated nitriles.

Exploratory optimizations revealed a delicate dependence on the nature of the base, palladium source, and ligand for sequential deprotonation–arylations. Optimally, treating a benzylic nitrile such as **2a** with TMPZnCl·LiCl (**1**: 1.5 equiv, THF, 25 °C, 10 min) followed by the addition of $Pd(OAc)_2$ (2 mol %), SPhos ligand[11] (4 mol %), and ethyl 4-bromobenzoate (**3a**: 0.8 equiv, 50 °C, 4 h) produces the mono-α-arylated product **4a** as the sole product in 83% yield (Table 1, entry 1). This procedure proved to be general and is applicable to benzylic nitriles bearing either an electron-withdrawing group (**2a**,**b**) or an electron-donating group (**2c**). Consequently, the reaction with various aryl bromides (**3a–c**) affords the arylated nitriles **4a–e** in 79–89% yield (Table 1).

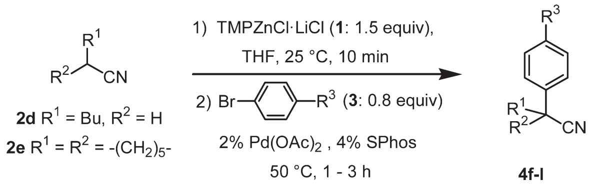
Table 1. α-Arylation of Benzylic Nitriles with TMPZnCl·LiCl

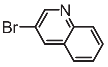


entry	2	3	4 yield (%)[a]
1	**2a**, $R^1 = CO_2Et$	**3a**, $R^2 = CO_2Et$	**4a** (83)
2	**2a**, $R^1 = CO_2Et$	**3c**, R^2 = OMe	**4b** (89)[b]
3	**2b**, R^1 = CN	**3a**, $R^2 = CO_2Et$	**4c** (80)
4	**2c**, R^1 = OMe	**3a**, $R^2 = CO_2Et$	**4d** (79)
5	**2c**, R^1 = OMe	**3b**, R^2 = CN	**4e** (85)

[a] Yield of isolated analytically pure product. [b] 2.0 equiv of TMPZnCl·LiCl was used.

Table 2. α-Arylation of Aliphatic Nitriles with TMPZnCl·LiCl



entry	2	3	4 yield (%)[a]
1	**2d**	**3d** $R^3 = NH_2$	**4f** (74)
2	**2d**	**3a** $R^3 = CO_2Et$	**4g** (77)
3	**2d**	**3b** R^3 = CN	**4h** (80)
4	**2d**	**3c** R^3 = OMe	**4i** (80)
5	**2d**	**3e** 	**4j** (64)[b]
6	**2e**	**3c** R^3 = OMe	**4k** (92)
7	**2e**	**3b** R^3 = CN	**4l** (73)

[a] Yield of isolated analytically pure product. [b] The reaction time for this example was 26 h.

A competitive bis-arylation of aliphatic nitriles may complicate the reaction outcome. Verkade has shown the utility of a bicyclic proazaphosphatrane for selectively performing the mono-arylation of metalated nitriles.[5d] Hartwig developed a more general approach using trimethylsilylalkylnitriles in the presence of ZnF_2 for avoiding bis-arylation.[5c] Interestingly, by using TMPZnCl·LiCl as a base, the primary aliphatic nitrile valeronitrile (**2d**) undergoes a selective mono-arylation with 4-bromoaniline (**3d**: 0.8 equiv, THF, 50 °C, 2 h) and $Pd(OAc)_2$ (2 mol %), SPhos (4 mol %) yielding the aniline derivative (**4f**) in 74% yield. Remarkably, a free NH_2- group in the aryl bromide (**3d**) is well tolerated (Table 2, entry 1). This selective mono-arylation occurs with various functionalized aryl and heteroaryl bromides (**3a–e**) furnishing the arylated nitriles (**4g–j**) in 64–89% yield (Table 2, entries 2–5). As expected, the prototypical cyclic nitrile, cyclohexanecarbonitrile (**2e**), reacts under the same conditions ($Pd(OAc)_2$ (2 mol %), SPhos (4 mol %)) with the aryl bromides **3b**,**c** (0.8 equiv, 50 °C, 3 h) to afford nitriles (**4k**,***l***) efficiently in 73–92% isolated yield (Table 2, entries 6 and 7). In contrast to previous nitrile arylations,[5a–d] the use of TMPZnCl·LiCl (**1**) allows cross-coupling under milder conditions (50 °C) and with shorter reaction times. Also,

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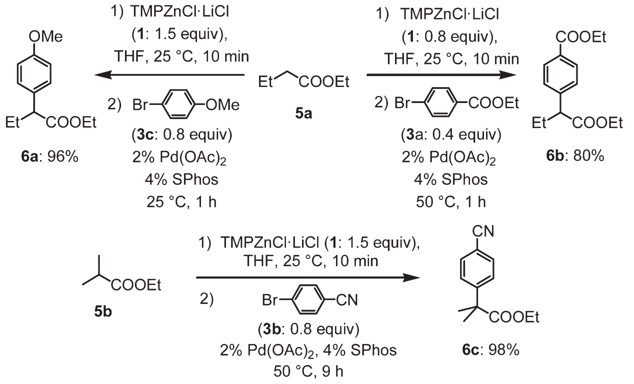
Scheme 1. α-Arylation of Ethyl Esters



sensitive ester and nitrile substituents are tolerated in the aryl bromides.

Prior palladium-catalyzed arylations of primary esters often required the sterically protected *tert*-butyl esters.[4d−j] Under our new conditions using TMPZnCl·LiCl (**1**), arylations are readily performed with *ethyl* esters. Thus, the reaction of ethyl butyrate (**5a**: 1.0 equiv) with TMPZnCl·LiCl (**1**: 1.5 equiv, THF, 25 °C, 10 min) followed by the addition of Pd(OAc)$_2$ (2 mol %), SPhos (4 mol %), and 4-bromoanisole **3c** (0.8 equiv, 25 °C, 1 h) provides the polyfunctional arylated ester (**6a**) in 96% isolated yield (Scheme 1). The presence of an ethyl ester in the aryl bromide is also tolerated, providing that the reaction is performed at 50 °C with 2 equiv of ethyl butyrate (**5a**). With these modifications, the expected arylated ethyl ester (**6b**) is isolated in 80% yield.[12] Similarly, the *secondary ester* ethyl isobutyrate (**5b**) undergoes the expected cross-coupling at 50 °C giving the α-arylated ethyl ester (**6c**) in quantitative yield (Scheme 1).

γ-Arylation reactions of α,β-unsaturated carbonyl compounds have been well-studied for unsaturated ketone or aldehydes.[13] Only recently have γ-arylations been examined with unsaturated esters.[6] Using TMPZnCl·LiCl (**1**), we have performed the first arylations of α,β- and β,γ-unsaturated nitriles and observe an exceptionally regioselective γ-arylation. Thus, the reaction of cyclohexene-1-carbonitrile (**7a**: 1.0 equiv) with TMPZnCl·LiCl (**1**: 2.0 equiv, THF, 25 °C, 10 min) followed by the addition of 4-bromoanisole (**3c**: 0.8 equiv) and the usual catalytic system at 50 °C for 1 h furnishes *regioselectively* the γ-arylated cyclohexene carbonitrile (**8a**) in 95% yield (Scheme 2). Performing the arylation reaction with the isomeric β,γ-unsaturated nitrile cyclohexene-2-carbonitrile (**9**) led under the same conditions to **8a** in 80% yield. This somewhat lower yield was attributed to the self-condensation reaction of **9**.[14] This side reaction could be avoided by adding the base TMPZnCl·LiCl (**1**) to a mixture of the nitrile **9**, the aryl bromide **3c**, and the Pd-catalytic system at 25 °C and stirring the reaction mixture at 50 °C for 1 h. Under these optimized conditions, the γ-arylated nitrile **8a** is obtained in 94% yield (Scheme 2).

Scheme 2. γ-Arylation of Unsaturated Nitriles (**7a** or **9**) with an Aryl Bromide (**3c**)

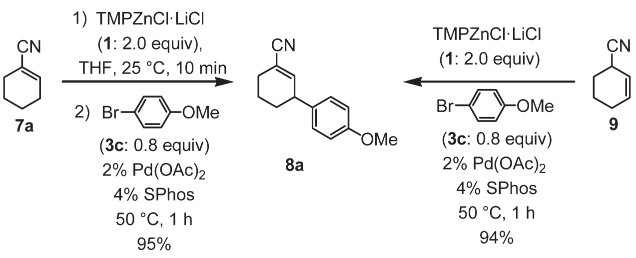
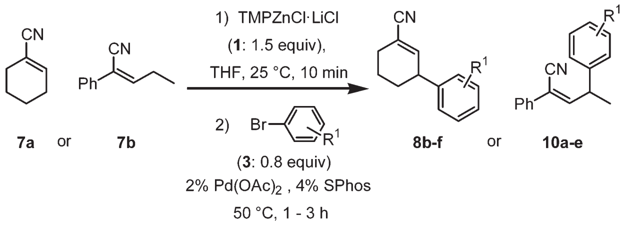
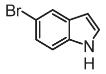


Table 3. γ-Arylation of Unsaturated Nitriles



entry	7	3	8 or 10 yield (%)[a]
1	**7a**	**3f** R^1 = 3-Cl	**8b** (72)
2	**7a**	**3g** R^1 = 3-CO$_2$Et	**8c** (69)
3	**7a**	**3h** R^1 = 4-F	**8d** (74)
4	**7a**	**3b** R^1 = 4-CN	**8e** (67)[b]
5	**7a**	**3i** 	**8f** (60)
6	**7b**	**3b** R^1 = 4-CN	**10a** (66)[c]
7	**7b**	**3c** R^1 = 4-OMe	**10b** (76)[c]
8	**7b**	**3j** R^1 = 4-Cl	**10c** (69)[d]
9	**7b**	**3k** R^1 = 4-NMe$_2$	**10d** (72)[d]
10	**7b**	**3l** R^1 = 4-TMS	**10e** (55)[d]

[a] Yield of isolated analytically pure product. [b] The double bond is conjugated with the aromatic ring. [c] 2.0 equiv of nitrile was used. [d] 2.5 equiv of nitrile was added over 60 min to the reaction mixture.

The arylation of alkenenitriles is similarly effective for a range of aryl bromides bearing various functional groups (Table 3, CO$_2$Et, Cl, F: **3f−h**) giving the γ-arylated α,β-unsaturated nitriles **8b−d** in 69−74% yield (Table 3,

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(12) Performing the arylation reaction at 25 °C results in extensive addition reactions of the intermediate zinc enolate to the ester function of **3a**. Conducting the reaction at 50 °C with 2 equiv of **5a** leads to the best results. This may be explained by a higher catalyst activity at this temperature.

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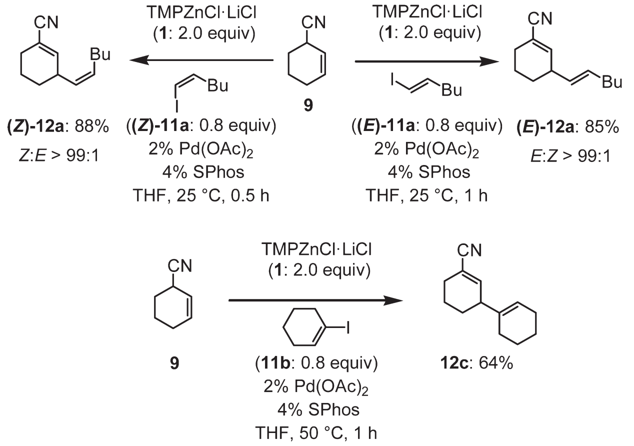
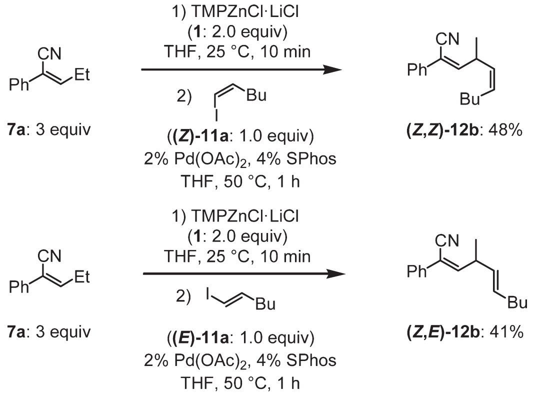
Scheme 3. Stereo- and Regioselective (*E*) and (*Z*) γ-Alkenylation of the Unsaturated Nitrile **9**



Scheme 4. Stereo- and Regioselective (*E*) and (*Z*) γ-Alkenylation of the Unsaturated Nitrile **7a**



entries 1–3). Interestingly, in the case of 4- bromobenzonitrile (**3b**), the γ-arylation occurs with concomitant migration of the double bond into conjugation with the aromatic ring, furnishing the allylic nitrile **8e** in 67% yield (Table 3, entry 4). Cross-coupling of cyclohexene-1-carbonitrile **7a** with the unprotected 5-bromoindole (**3i**) leads to the functionalized indole (**8f**) in 60% yield (Table 3, entry 5). The open-chain 2-phenyl-substituted α,β-unsaturated nitrile (*Z*)-2-phenylpent-2-enenitrile (**7b**) reacts similarly under the same conditions. Coupling **7b** with various aryl bromides (**3b**,**c**, **3j**–***l***) provides the γ-arylated *Z*-unsaturated nitriles **10a**–**e** in 55–76% yield, maintaining the olefin stereochemistry (Table 3, entries 6–10).

In contrast to enolate arylations, the corresponding alkenylation is particularly rare[6,15] and is unknown for nitriles. The alkenylation of unsaturated nitriles **7b** and **9** was readily achieved with TMPZnCl·LiCl (**1**) with complete γ-regioselectivity. Thus, the reaction of the β,γ-unsaturated nitrile **9** (1.0 equiv) with either (*E*)- or (*Z*)-1-iodohex-1-ene ((*E*)- or (*Z*)-**11a**) affords the corresponding unsaturated nitriles (*E*)-**12a** and (*Z*)-**12a** in 85–88% yield with perfect retention of the double bond stereochemistry (Scheme 3). Increasing the steric demand in the alkenyl iodide is similarly effective with the Pd-catalyzed reaction of 1-iodocyclohex-1-ene **11b** and cyclohex-2-enecarbonitrile (**9**) giving the diene nitrile **12c** in 64% yield (Scheme 3).

In the case of the α,β-unsaturated nitrile (**7b**), the configuration of both double bonds is controlled, furnishing after the reaction with *E*- or *Z*-**11a** the (*Z*,*Z*) and (*Z*,*E*) skipped dienes (*Z*,*Z*)-**12b** and (*Z*,*E*)-**12b** with high diastereoselectivity (> 99% (*Z*,*Z*) or (*Z*,*E*)) (Scheme 4).

In summary, we have reported a practical Pd-catalyzed arylation of zincated nitriles and ester enolates with diverse, functionalized aryl bromides. Highly regioselective γ-arylation or γ-alkenylation of α,β- or β,γ-unsaturated nitriles faithfully translate the vinyl iodide and unsaturated nitrile stereochemistry into a variety of γ-substituted unsaturated nitriles.

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Supporting Information Available. Experimental procedures and full characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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