ORGANIC LETTERS
2011
Vol. 13, No. 7
1690–1693

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

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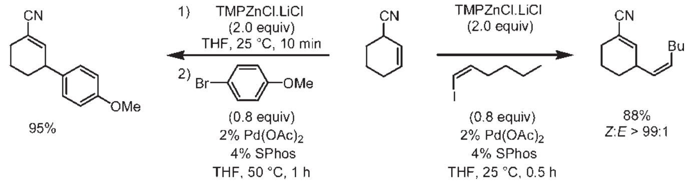
Received January 21, 2011

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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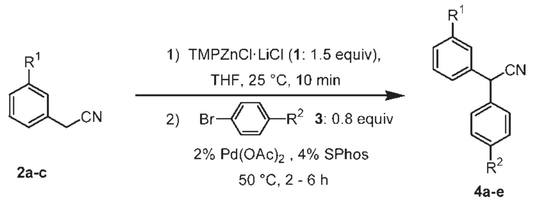
performed Pd-catalyzed cross-couplings using Pd_2dba_3 and tBu_3P as catalytic system.[6] The choice of the appropriate base, the palladium catalyst, and the reaction conditions is essential for obtaining high yields. Recently, Hartwig reported silyl ketene acetals as enolate equivalents in a new Pd-catalyzed 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 iPr_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).

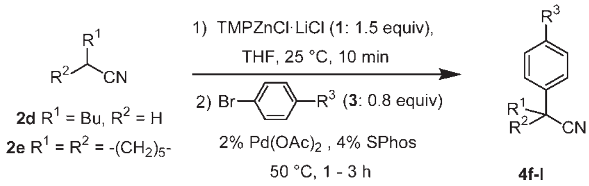
Table 1. α-Arylation of Benzylic Nitriles with TMPZnCl·LiCl

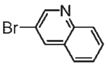


entry	2	3	4 yield (%)[a]
1	**2a**, $R^1 = CO_2Et$	**3a**, $R^2 = CO_2Et$	**4a** (83)
2	**2a**, $R^1 = CO_2Et$	**3c**, $R^2 = OMe$	**4b** (89)[b]
3	**2b**, $R^1 = CN$	**3a**, $R^2 = CO_2Et$	**4c** (80)
4	**2c**, $R^1 = OMe$	**3a**, $R^2 = CO_2Et$	**4d** (79)
5	**2c**, $R^1 = OMe$	**3b**, $R^2 = CN$	**4e** (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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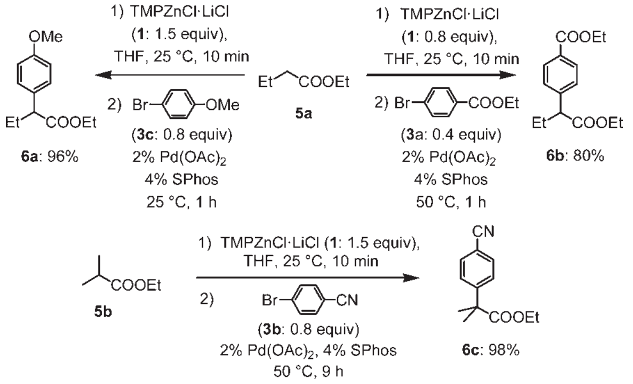
Scheme 1. α-Arylation of Ethyl Esters



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

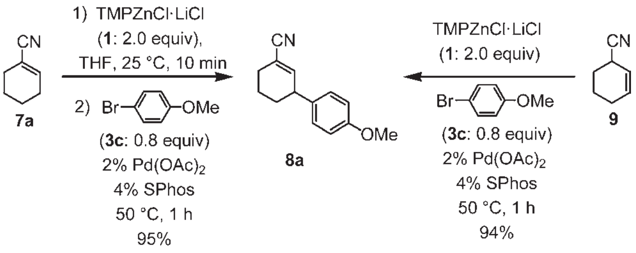
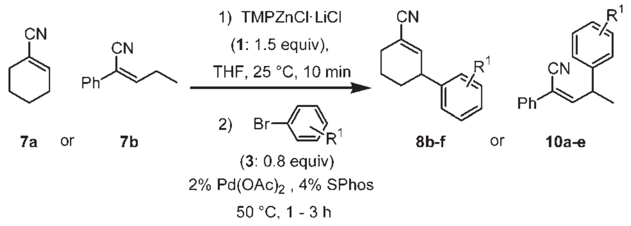
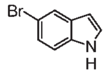


Table 3. γ-Arylation of Unsaturated Nitriles



entry	7	3	8 or 10 yield (%)[a]
1	**7a**	**3f** R^1 = 3-Cl	**8b** (72)
2	**7a**	**3g** R^1 = 3-CO_2Et	**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.

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).

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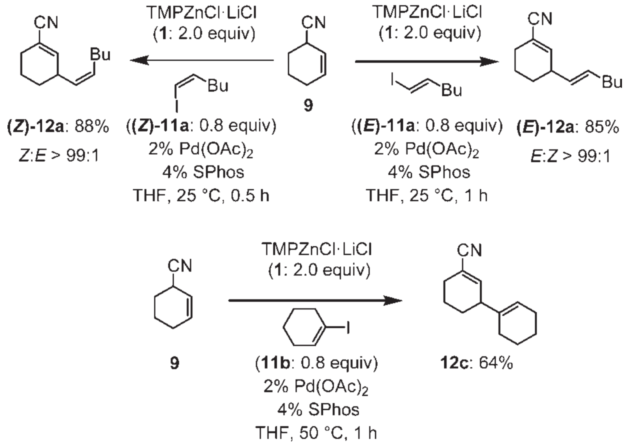
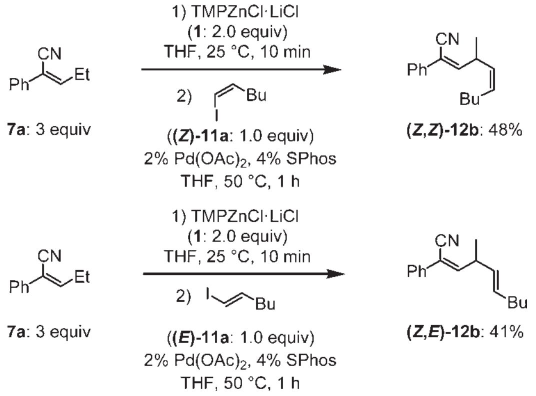
Scheme 3. Stereo- and Regioselective (*E*) and (*Z*) γ-Alkenylation of the Unsaturated Nitrile **9**



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).

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



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.

Acknowledgment. We thank the Fonds der Chemischen Industrie, the European Research Council (ERC), and the Deutsche Forschungsgemeinschaft (DFG) for financial support. Prof. F. Fleming thanks the Center of Advanced Studies, Ludwig Maximilians-Universität München (CAS) for a visiting professor fellowship. We also thank BASF AG (Ludwigshafen) and Chemetall GmbH (Frankfurt) for the generous gift of chemicals.

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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