Communications

Synthetic Methods

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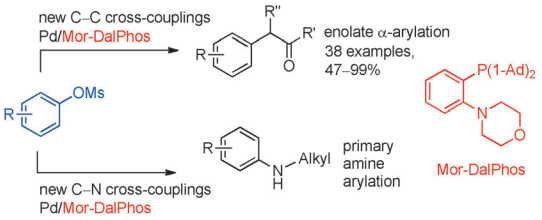
Addressing Challenges in Palladium-Catalyzed Cross-Couplings of Aryl Mesylates: Monoarylation of Ketones and Primary Alkyl Amines



Mor(DalPhos) for Me(sylates): Described are the first examples of ketone mono-α-arylation and primary aliphatic amine monoarylation employing aryl methanesulfonate coupling partners. A range of functionalized aryl mesylates were employed with dialkyl ketones, and also with primary and secondary amines as well as the otherwise challenging coupling partners acetone and methylamine. Ad = adamantyl.

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Addressing Challenges in Palladium-Catalyzed Cross-Couplings of Aryl Mesylates: Monoarylation of Ketones and Primary Alkyl Amines**

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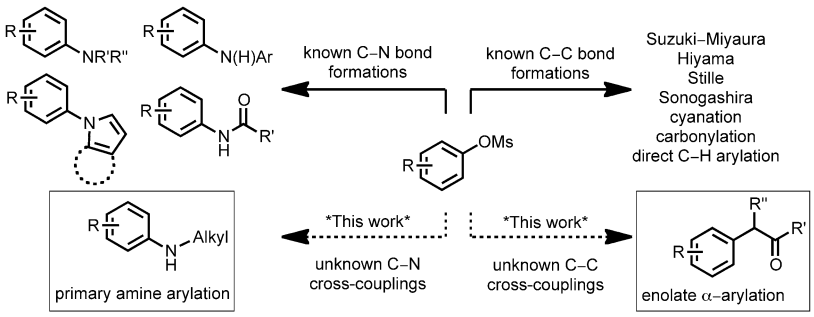
The development of palladium-catalyzed bond-forming processes has revolutionized modern organic synthesis.[1] The Nobel Prize winning developments of Heck, Negishi, and Suzuki in palladium-catalyzed C–C cross-coupling chemistry have led to a diversity of alternative and effective C–C and C–X (X = N, O, S, etc.) bond-forming protocols.[2] In this process, the optimization of reaction conditions, including the palladium source and ligand has enabled otherwise challenging electrophilic coupling partners to be accommodated,[3] including aryl chlorides and pseudohalides. Despite this significant progress, comparatively few catalyst systems applicable to aryl methanesulfonates (mesylates) have been reported. The identification of suitable catalytic conditions that facilitate turnover of the aryl mesylate while circumventing phenol formation has proven to be a daunting challenge. Nonetheless, significant interest in the use of aryl mesylates as reaction partners persists owing to their low cost, high stability, and greater atom economy in comparison to related aryl tosylates and triflates.[4] Furthermore, the derived byproduct, methanesulfonic acid, from the cross-coupling is naturally occurring and undergoes biodegradation in wastewater processing.[5]

The use of aryl mesylates in palladium-catalyzed C–C cross-couplings, including but not restricted to Suzuki–Miyaura, Stille, and Sonogashira reactions, has been described.[4] Conversely, the successful application of aryl mesylates in an analogous enolate α-arylation, a powerful and complementary reaction class developed by the groups of Buchwald,[6] Hartwig[7] and others,[8] has yet to be reported (Scheme 1). Moreover, while a small number of publications by Kwong and co-workers[9] and Buchwald and co-workers[10] detailing the use of aryl mesylates in the now-ubiquitous Buchwald–Hartwig amination have appeared, these are limited to the arylation of anilines, amides, pyrroles, and secondary alkyl amines. Cross-couplings of primary aliphatic amines and aryl mesylates have not been reported (Scheme 1). Given that palladium-catalyzed enolate α-arylation and Buchwald–Hartwig amination are among the most widely utilized C–C and C–N bond-forming methods, the identification of catalysts capable of accommodating aryl mesylates in such processes represents a desirable target to further expand the scope of these protocols.

Herein we report the first examples of enolate mono-α-arylation chemistry, wherein aryl mesylate coupling partners are employed in combination with cyclic and acyclic dialkyl ketones. We also present the first Buchwald–Hartwig amination reactions involving primary aliphatic amine and aryl mesylate coupling partners.

The mono-α-arylation of carbonyl compounds with (hetero)aryl (pseudo)halides represents a useful C–C bond-forming reaction which has been applied to a range of substrates having acidic α C–H moieties.[11] Regarding the parent ketone, acetone, mono-α-arylation has posed a particular challenge, and has been addressed only recently. The first examples of acetone mono-α-arylation were reported by our group[12] and employ the [{Pd(cinnamyl)Cl}$_2$]/Mor-DalPhos (see Scheme 2 for structure) catalyst system in combination with both (hetero)aryl halides and tosylates. Subsequently, Ackermann and Mehta[13] reported the use of a Pd/XantPhos catalyst for the coupling of aryl imidazolylsulfonates with acetone and other ketones.[14] Encouraged by the desirable performance of [{Pd(cinnamyl)Cl}$_2$]/Mor-DalPhos in this context,[12,15] we initially directed our efforts towards the



Scheme 1. Scope of C–C and C–N cross-couplings of aryl mesylates, and reactions featured in this report.

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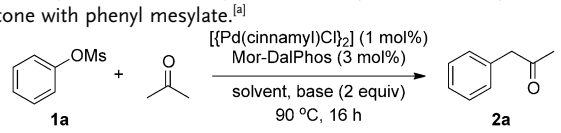
Table 1: Optimization of the palladium-catalyzed mono-α-arylation of acetone with phenyl mesylate.[a]



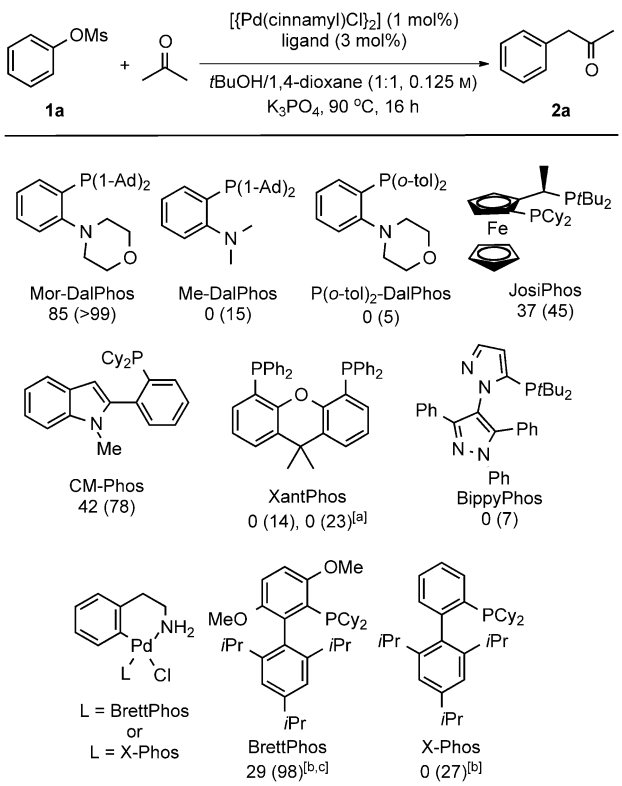
Entry	Solvent (*x* M)	Base	Conv. [%]	Yield [%]
1	acetone (0.5 M)	Cs_2CO_3	>99	54
2	acetone (0.5 M)	K_3PO_4	95	43
3	1,4-dioxane (0.5 M)	Cs_2CO_3	81	33
4	*t*BuOH (0.5 M)	Cs_2CO_3	>99	14
5[b]	*t*BuOH (0.5 M)	K_3PO_4	>99	78, 56
6[b]	*t*BuOH (0.125 M)	K_3PO_4	>99	87, 84
7[b]	*t*BuOH/1,4-dioxane (1:1; 0.125 M)	K_3PO_4	>99	79, 79
8[b]	*t*BuOH/1,4-dioxane (1:1; 0.125 M)	K_3PO_4	>99	85, 85
9	*t*BuOH/1,4-dioxane (1:1; 0.125 M)	CsF	38	24
10[c]	*t*BuOH/1,4-dioxane (1:1; 0.125 M)	NaO*t*Bu	>99	4

[a] Reaction conditions: 0.2–0.4 mmol **1a** ([**1a**] = x M), 10 equiv acetone except for entries 1 and 2, [Pd]/L ratio = 2:3. Conversions and yields determined on the basis of calibrated GC data of **1a** and **2a** using dodecane as an internal standard. [b] Yields of duplicate reactions provided. [c] Phenol observed as the major side product. Ms = methanesulfonyl.

identification of suitable reaction conditions employing this catalyst system for the hitherto unknown mono-α-arylation of acetone with phenyl mesylate (**1a**) to form phenylacetone (**2a**; Table 1). Central to this effort was the quest to identify a base/catalyst pairing which would promote the desired acetone mono-α-arylation reaction while avoiding phenol formation.

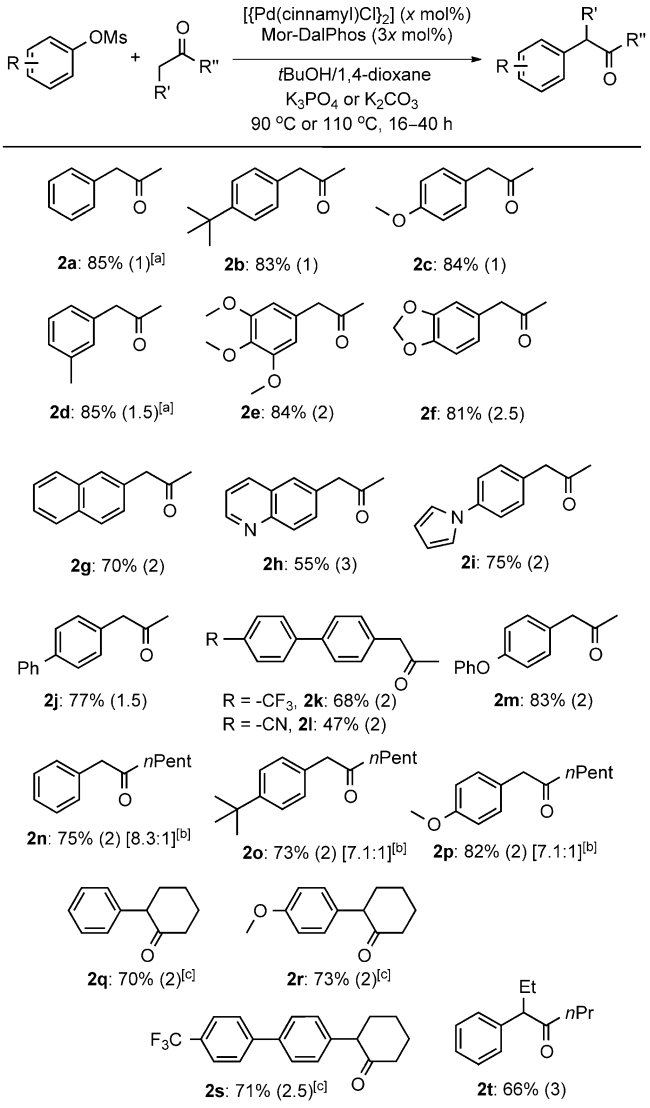
In adapting our previously optimized reaction conditions established for the mono-α-arylation of acetone with aryl halides and tosylates,[12] the use of 1 mol% [{Pd(cinnamyl)Cl}$_2$], 3 mol% Mor-DalPhos, and Cs_2CO_3 as a base in acetone (Table 1, entry 1) resulted in full conversion of **1a**, thus affording the target product **2a** in 54% (GC yield). Substituting K_3PO_4 as the base resulted in high conversion but a slightly lower yield of **2a** (Table 1, entry 2). At a relatively high concentration of **1a** (0.5 M), high conversions but low yields resulted from either the use of 1,4-dioxane or *tert*-butanol with 10 equivalents of acetone. (Table 1, entries 3 and 4). Replacing Cs_2CO_3 with K_3PO_4 in *tert*-butanol allowed both full conversion and a significant increase in the GC yield of **2a** (Table 1, entry 5). However, performing this reaction in duplicate gave inconsistent yields (78 versus 56%), which we believe to be a result of the reactions forming very viscous, nonuniform mixtures upon heating. To circumvent these issues, the reaction concentration was decreased to 0.125 M using *tert*-butanol (Table 1, entry 6), thus resulting in high and reproducible yields of **2a**. However, the reaction mixtures continued to become viscous, thereby preventing uniform stirring. Employing 1,4-dioxane under these dilute conditions allowed more uniform stirring but gave a slightly lower, albeit reproducible yield for **2a** (Table 1, entry 7). Thus we elected to employ these two solvents together in a 1:1 ratio. Under these reaction conditions **2a** was obtained in reproducible GC yields of 85% (Table 1, entry 8). Performing the reaction in the absence of ligand or palladium resulted in approximately 50% conversion of **1a**, with no formation of **2a** observed. Alternative bases were also tested under these optimal solvent conditions (Table 1, entries 9 and 10) but were shown to give poor conversion of **1a** or low yield of **2a**, thereby establishing K_3PO_4 as the optimal base for this transformation.

In an effort to assess the influence of the ancillary ligand on the course of reaction, a judiciously selected range of mono- and bisphosphines, which have proven effective in the palladium-catalyzed α-arylation of carbonyl compounds, in Buchwald–Hartwig amination, and in alternative cross-coupling applications employing aryl mesylates, were tested under the optimized reaction conditions (Scheme 2). Both Me-DalPhos and P(*o*-tol)$_2$-DalPhos afforded minimal conversion and none of the desired product **2a**. Similarly poor results were obtained with XantPhos (under the optimized reaction conditions described herein or under previously reported conditions[13]), BippyPhos, and a palladacycle/X-Phos catalyst. Furthermore, the use of the JosiPhos variant CyPF*t*Bu, or ligands used to facilitate C–N cross-coupling reactions of aryl mesylates (CM-Phos and BrettPhos), afforded **2a** (29–42% yield), but the yields were inferior to those obtained when using the Mor-DalPhos-based catalyst.



Scheme 2. Ligand comparisons in the mono-α-arylation of acetone with phenyl mesylate. Reaction conditions: 0.4 mmol **1a**, 10 equiv acetone, [Pd]/L ratio = 2:3. Yields (conversions in parentheses) determined on the basis of calibrated GC data of **1a** and **2a** using dodecane as an internal standard. Phenol is the major side product in most cases. [a] Used 5 mol% Pd(OAc)$_2$, 10 mol% XantPhos, 14 equiv acetone, 2 equiv Cs_2CO_3, 1,4-dioxane (0.25 M), 80 °C. [b] Used 2 mol% palladacycle, 2 mol% ligand. [c] Significant polyarylation observed. Ad = adamantlyl.

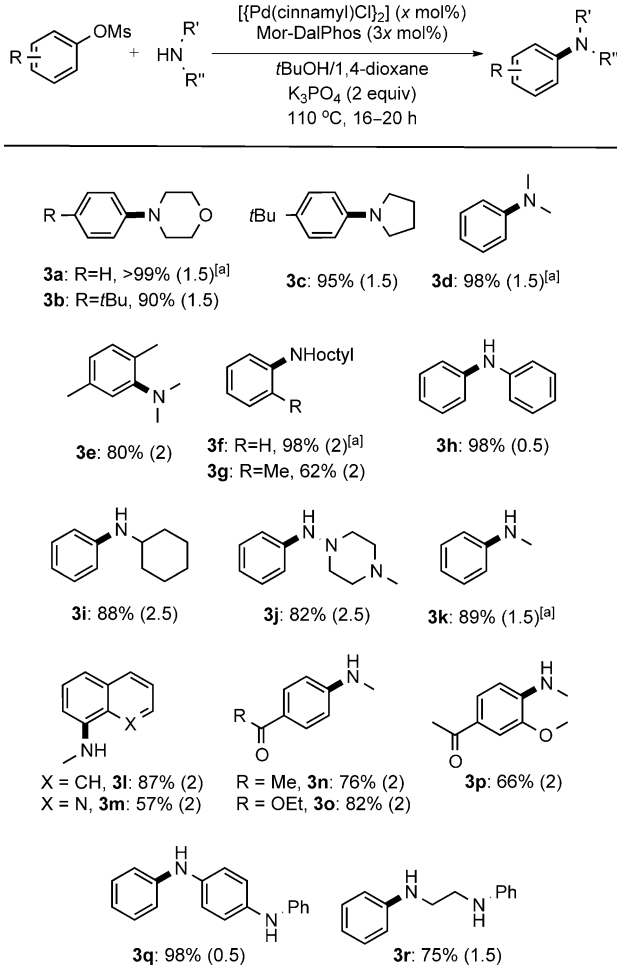
Having established the suitability of the [{Pd(cinnamyl)Cl}$_2$]/Mor-DalPhos catalyst system as well as optimal reaction conditions for the coupling of acetone and phenyl mesylate, the scope of aryl mesylates was then explored in the mono-α-arylation of acetone (Scheme 3). Electron-neutral and electron-rich aryl mesylates were well tolerated in the reaction, thus affording greater than 80% yields of the benzyl methyl ketone products **2a–f**. Fused-aryl mesylate substrates also proved to be good reaction partners (**2g** and **2h**), including a quinoline derivative. Substituted (hetero)biaryl benzyl ketone derivatives were also prepared in this manner (**2i–l**), thus demonstrating the tolerance of pyrrole (**2i**), 4-trifluoromethylphenyl (**2k**), and 4-benzonitrile (**2l**) substituents within the mesylate reagent. A 4-phenoxyphenyl-derived product (**2m**) was also obtained in high yield upon isolation (83%; compare to the more electron-rich 4-methoxy analogue **2c**, 84%).



Scheme 3. Scope of the palladium-catalyzed α-arylation of ketones with aryl mesylates. Reaction conditions: 0.6–0.8 mmol ArOMs, 5–10 equiv ketone, [Pd]/L = 2:3, [ArOMs] = 0.5–0.125 M. See the Supporting Information. Yields are of isolated material, and mol% [{Pd(cinnamyl)Cl}$_2$] is indicated within parentheses. [a] Yield determined on the basis of calibrated GC data of **2a** and **2d** using dodecane as an internal standard. [b] Mixture of regioisomers. Ratio indicated within brackets, with major product shown. [c] Used *tert*-butanol solvent, K_2CO_3, 110°C.

Efforts to optimize the established conditions to allow the accommodation of electron-poor and *ortho*-substituted aryl mesylates were unsuccessful, mainly resulting in decomposition of the starting materials to the corresponding aryl alcohol. Nevertheless, the scope was extended to the use of other linear and cyclic aliphatic ketones. 2-Heptanone and cyclohexanone were found to be suitable coupling partners, thus affording the desired benzyl ketones in high isolated yields (**2n–s**). For the products formed from 2-heptanone (**2n–p**), a mixture of regioisomers was obtained in each case, where the major product corresponded to monoarylation at the α-methyl position and the minor at the α-CH_2-C_4H_9 of the ketone (determined on the basis of ^{1}H NMR data). These products could not be easily separated by use of column chromatography. Changing the base to K_2CO_3 at 110°C (0.5 M [ArOMs] in *tert*-butanol) allowed cyclohexanone mono-α-arylation (**2q–s**). Additionally, 4-heptanone was accommodated in this chemistry under more forcing reaction conditions, thus providing **2t** in 66% yield upon isolation. Attempts to α-arylate acetophenone were successful to a certain extent, that is, employing CsF as the base afforded 68% yield of a mixture of mono- and diarylation products in a 7.6:1 ratio favoring mono-α-arylation. Thus, further optimization is required to promote the selective mono-α-arylation of aryl ketone coupling partners.

Encouraged by our success in developing the first examples of enolate α-arylation employing aryl mesylate coupling partners, we turned our attention to expanding the scope of Buchwald–Hartwig amination chemistry involving such challenging electrophiles using [{Pd(cinnamyl)Cl}$_2$]/Mor-DalPhos.[16] Although a vast combination of (hetero)aryl (pseudo)halides and amines can be cross-coupled by using established Buchwald–Hartwig amination methods, the scope of phenol-derived (hetero)aryl electrophiles, which have been successfully employed thus far, is limited almost exclusively to benzenesulfonates, tosylates, triflates, and nonaflates.[4a,b,17] Only two research groups have achieved C–N cross-coupling reactions of aryl mesylates.[9,10] Kwong and co-workers first reported the coupling of anilines and secondary amines with aryl mesylates employing a Pd/CM-Phos catalyst system,[9] and the scope of the amine reaction partner was limited primarily to anilines and pyrrolic amines, with only three examples of secondary aliphatic amines, and no examples involving primary alkyl amines. Soon after, Buchwald and co-workers reported the use of the Pd/BrettPhos catalyst system for the coupling of aryl mesylates with anilines, in which six examples in total were presented.[10a] More recently, the Pd/X-Phos catalyst system has been shown to effectively couple amides with a variety of aryl mesylate partners.[10b] Given the absence of literature reports of the cross-coupling of primary aliphatic amines and aryl mesylates, as well as the limited number of transformations involving secondary dialkyl amines, we sought to address these substrate scope limitations by applying our optimized aryl mesylate coupling conditions (Scheme 4).



Scheme 4. Scope of the palladium-catalyzed amination of aryl mesylates. Reaction conditions: 0.6–1.0 mmol ArOMs, 1.1–5 equiv amine, [Pd]/L = 2:3, [ArOMs] = 0.25–0.1 M. See the Supporting Information. Yields are of isolated material, and mol% [{Pd(cinnamyl)Cl}$_2$] indicated within parentheses. [a] Yield determined on the basis of calibrated GC data of **3a**, **3d**, **3f**, and **3k** using dodecane as an internal standard.

We were pleased to find that cyclic dialkyl amines such as morpholine (**3a** and **3b**) and piperidine (**3c**) afforded the corresponding aryl amines in excellent yields. Dimethylamine performed similarly well both with phenyl mesylate producing **3d** (98%), as well as with a xylyl mesylate where the derived volatile aryl amine **3e** was obtained in high yield upon isolation (80%). Notably, octylamine was well tolerated in reactions employing either the parent aryl mesylate **1a** (98% yield of **3f**) or the more sterically hindered *o*-tolyl mesylate (62% yield of **3g**). Aniline, serving as a representative example of primary aromatic amines, proved to be a favorable reaction partner in this system, thus requiring low catalyst loading (1 mol% Pd) and achieving nearly quantitative yield of diphenylamine (**3h**). Both cyclohexylamine and the hydrazine derivative 1-amino-4-methylpiperazine, were also mono-N-arylated successfully, each in greater than 80% yield upon isolation (**3i** and **3j**).

In select cases, reactions employing morpholine, dimethylamine, or octylamine in combination with sterically hindered or electron-deficient aryl mesylates resulted in minimal formation of the desired aniline derivative because of the competing background reactions involving sulfonyl transfer.[18] However, methylamine, which can be a challenging substrate in its own right in Buchwald–Hartwig amination chemistry,[10a,16c,19] was employed without difficulty in cross-coupling reactions involving aryl mesylates featuring *ortho* substitutents and electron-withdrawing groups. The standard reaction of methylamine with phenyl mesylate proceeded cleanly, thus affording the target aniline **3k** in high yield, as did the analogous reaction leading to the naphthyl derivative **3l**. The 8-quinolinyl mesylate was also tolerated in this chemistry (**3m**). The acetophenone derivatives **3n** and **3p** were synthesized in good yields, thereby establishing the ability to conduct N–H arylation reactions chemoselectively in the presence of functionality featuring enolizable protons as well as electron-withdrawing, base-sensitive functional groups. Additional functional-group tolerance was established in the synthesis of the ethyl ester **3o** (82%). Finally, substrates containing two potentially reactive NH sites were selectively monoarylated at the primary amine sites (**3q** and **3r**), thereby further demonstrating the chemoselective capabilities of this transformation.

In summary, we have disclosed the first examples of ketone mono-α-arylation using aryl mesylates and have also successfully demonstrated for the first time the amination of these inexpensive phenol derivatives with primary aliphatic amines. The [{Pd(cinnamyl)Cl}$_2$]/Mor-DalPhos catalyst system allowed a range of substituted aryl mesylates to be coupled with both cyclic and acyclic dialkyl ketones, including acetone, which is normally a challenging reagent in mono-α-arylation chemistry. Applying these optimized ketone α-arylation conditions to Buchwald–Hartwig amination enabled the mono-N-arylation of primary and secondary aliphatic amines, including methylamine, by employing aryl mesylates featuring electron-donating or electron-withdrawing functionality, *ortho*-substitution, as well as base-sensitive groups. Furthermore, the amination protocol displayed chemoselectivity, thus favoring cross-coupling of the primary amine in each case. We are continuing to examine the role of catalyst design in expanding the scope of nucleophilic reaction partners with challenging nonhalide aryl electrophiles in cross-coupling chemistry, and will disclose our progress in future reports.

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[1] a) S. Bräse, A. D. Meijere in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: A. d. Meijere, F. Diederich), Wiley-VCH, Weinheim, **2008**, pp. 217–315; b) N. Miyaura in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2008**, pp. 41–123; c) J. F. Hartwig, *Organotransition Metal Chemistry*, University Science Books, Sausalito, CA, **2010**; d) C. L. Allen, J. M. J. Williams, *Chem. Soc. Rev.* **2011**, *40*, 3405–3415.

[2] a) X.-F. Wu, P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem.* **2010**, *122*, 9231 – 9234; *Angew. Chem. Int. Ed.* **2010**, *49*, 9047 – 9050; b) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem.* **2012**, *124*, 5150 – 5174; *Angew. Chem. Int. Ed.* **2012**, *51*, 5062 – 5085.

[3] a) R. J. Lundgren, M. Stradiotto, *Chem. Eur. J.* **2012**, *18*, 9758 – 9769; b) C. Valente, S. Çalimsiz, K. H. Hoi, D. Mallik, M. Sayah, M. G. Organ, *Angew. Chem.* **2012**, *124*, 3370 – 3388; *Angew. Chem. Int. Ed.* **2012**, *51*, 3314 – 3332; c) S. M. Wong, C. M. So, F. Y. Kwong, *Synlett* **2012**, 1132 – 1153.

[4] For selected recent reports and reviews, see: a) C. M. So, F. Y. Kwong, *Chem. Soc. Rev.* **2011**, *40*, 4963 – 4972; b) B.-J. Li, D.-G. Yu, C.-L. Sun, Z.-J. Shi, *Chem. Eur. J.* **2011**, *17*, 1728 – 1759; c) S. I. Kozhushkov, H. K. Potukuchi, L. Ackermann, *Catal. Sci. Technol.* **2013**, *3*, 562 – 571; d) D. S. Lee, P. Y. Choy, C. M. So, J. Wang, C. P. Lau, F. Y. Kwong, *RSC Adv.* **2012**, *2*, 9179 – 9182; e) G. A. Molander, I. Shin, *Org. Lett.* **2012**, *14*, 3138 – 3141; f) B. Song, T. Knauber, L. J. Gooßen, *Angew. Chem.* **2013**, *125*, 3026 – 3030; *Angew. Chem. Int. Ed.* **2013**, *52*, 2954 – 2958.

[5] a) S. C. Baker, D. P. Kelly, J. C. Murrell, *Nature* **1991**, *350*, 627 – 628; b) E. S. Venkataramani, A. L. Forman, R. J. Magliette, Jr., W. A. Vaughn, R. R. Dauer, PCT Int. Appl. WO 9521135, **1995** (CAN 123:207938); c) A. Commarieu, W. Hoelderich, J. A. Laffitte, M.-P. Dupont, *J. Mol. Catal. A* **2002**, *182 – 183*, 137 – 141; d) M. C. Wilkinson, *Org. Lett.* **2011**, *13*, 2232 – 2235.

[6] a) M. Palucki, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 11108 – 11109; b) J. Åhman, J. P. Wolfe, M. V. Troutman, M. Palucki, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 1918 – 1919.

[7] a) B. C. Hamann, J. F. Hartwig, *J. Am. Chem. Soc.* **1997**, *119*, 12382 – 12383; b) K. H. Shaughnessy, B. C. Hamann, J. F. Hartwig, *J. Org. Chem.* **1998**, *63*, 6546 – 6553.

[8] T. Satoh, Y. Kawamura, M. Miura, M. Nomura, *Angew. Chem.* **1997**, *109*, 1820 – 1822; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1740 – 1742.

[9] C. M. So, Z. Zhou, C. P. Lau, F. Y. Kwong, *Angew. Chem.* **2008**, *120*, 6502 – 6506; *Angew. Chem. Int. Ed.* **2008**, *47*, 6402 – 6406.

[10] a) B. P. Fors, D. A. Watson, M. R. Biscoe, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 13552 – 13554; b) K. Dooleweerdt, B. P. Fors, S. L. Buchwald, *Org. Lett.* **2010**, *12*, 2350 – 2353.

[11] a) D. A. Culkin, J. F. Hartwig, *Acc. Chem. Res.* **2003**, *36*, 234 – 245; b) C. C. C. Johansson, T. J. Colacot, *Angew. Chem.* **2010**, *122*, 686 – 718; *Angew. Chem. Int. Ed.* **2010**, *49*, 676 – 707; c) F. Bellina, R. Rossi, *Chem. Rev.* **2010**, *110*, 1082 – 1146; d) P. Novak, R. Martin, *Curr. Org. Chem.* **2011**, *15*, 3233 – 3262.

[12] K. D. Hesp, R. J. Lundgren, M. Stradiotto, *J. Am. Chem. Soc.* **2011**, *133*, 5194 – 5197.

[13] L. Ackermann, V. P. Mehta, *Chem. Eur. J.* **2012**, *18*, 10230 – 10233.

[14] While this manuscript was under review, the following report was published in which an alternative P,N ligand was employed under reaction conditions identical to those previously reported by us for the coupling of aryl chlorides and acetone: P. Li, B. Lü, C. Fu, S. Ma, *Adv. Synth. Catal.* **2013**, *355*, 1255 – 1259.

[15] S. M. Crawford, P. G. Alsabeh, M. Stradiotto, *Eur. J. Org. Chem.* **2012**, 6042 – 6050.

[16] For selected reports featuring the [{Pd(cinnamyl)Cl}$_2$]/Mor-DalPhos catalyst system in challenging Buchwald–Hartwig aminations, see: a) R. J. Lundgren, B. D. Peters, P. G. Alsabeh, M. Stradiotto, *Angew. Chem.* **2010**, *122*, 4165 – 4168; *Angew. Chem. Int. Ed.* **2010**, *49*, 4071 – 4074; b) R. J. Lundgren, M. Stradiotto, *Angew. Chem.* **2010**, *122*, 8868 – 8872; *Angew. Chem. Int. Ed.* **2010**, *49*, 8686 – 8690; c) B. J. Tardiff, R. McDonald, M. J. Ferguson, M. Stradiotto, *J. Org. Chem.* **2012**, *77*, 1056 – 1071.

[17] For selected lead references and reviews, see: a) J. Louie, M. S. Driver, B. C. Hamann, J. F. Hartwig, *J. Org. Chem.* **1997**, *62*, 1268 – 1273; b) B. C. Hamann, J. F. Hartwig, *J. Am. Chem. Soc.* **1998**, *120*, 7369 – 7370; c) X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 6653 – 6655; d) K. W. Anderson, M. Mendez-Perez, J. Priego, S. L. Buchwald, *J. Org. Chem.* **2003**, *68*, 9563 – 9573; e) J. Högermeier, H.-U. Reissig, *Adv. Synth. Catal.* **2009**, *351*, 2747 – 2763; f) B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg, V. Percec, *Chem. Rev.* **2011**, *111*, 1346 – 1416.

[18] I. M. Gordon, H. Maskill, M.-F. Ruasse, *Chem. Soc. Rev.* **1989**, *18*, 123 – 151.

[19] For selected recent examples, see: a) R. J. Lundgren, A. Sappong-Kumankumah, M. Stradiotto, *Chem. Eur. J.* **2010**, *16*, 1983 – 1991; b) B. P. Fors, S. L. Buchwald, *J. Am. Chem. Soc.* **2010**, *132*, 15914 – 15917; c) P. G. Alsabeh, R. J. Lundgren, L. E. Longobardi, M. Stradiotto, *Chem. Commun.* **2011**, *47*, 6936 – 6938; d) C. B. Lavery, R. McDonald, M. Stradiotto, *Chem. Commun.* **2012**, *48*, 7277 – 7279.

