C–H Functionalization

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Use of a Readily Removable Auxiliary Group for the Synthesis of Pyrrolidones by the Palladium-Catalyzed Intramolecular Amination of Unactivated γ C(sp^3)–H Bonds**

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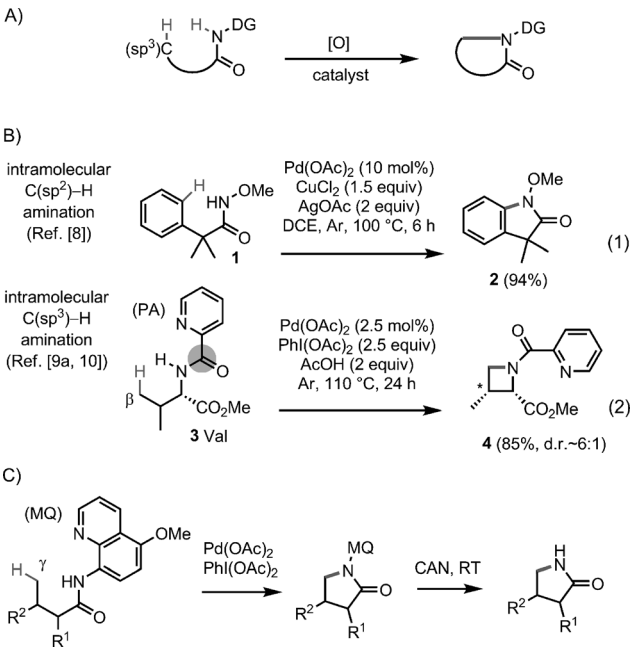
Medium-sized lactams are important structural motifs in natural products and pharmaceutical agents.[1] Although intramolecular amide-coupling reactions have been routinely used for lactamization, these methods require substrates that contain both free amino and carboxylic acid functional groups and often require additional protection/deprotection operations. In contrast, a strategy based on the intramolecular amination of C–H bonds could provide a straightforward approach to lactam products from readily available amide precursors and thus simplify substrate preparation and enable novel retrosynthetic planning (Scheme 1 A).[2–7] In a seminal report in 2008, Wasa and Yu disclosed their synthesis of γ- and δ-benzo-fused lactams through the palladium-catalyzed intramolecular amination of *ortho* C(sp^2)–H bonds of *N*-methoxyhydroxamic acids [Eq. (1), Scheme 1 B].[8] However, the synthesis of substituted pyrrolidinones by the metal-catalyzed amination of unactivated C(sp^3)–H bonds of aliphatic substrates has not yet been described. Herein, we report an efficient and readily applicable method for the synthesis of complex pyrrolidinones on the basis of the palladium-catalyzed carboxamide-directed intramolecular amination of unactivated γ C(sp^3)–H bonds (Scheme 1 C).

In 2012, Nadres and Daugulis as well as our research group reported a set of palladium-catalyzed, picolinamide-directed, and PhI(OAc)$_2$-mediated intramolecular amination reactions of unactivated C(sp^3)–H and C(sp^2)–H bonds of amine substrates to form azetidines, pyrrolidines, and indolines [Eq. (2), Scheme 1; PA = picolinamide].[9–11] Encouraged by this success, we proceeded to explore whether secondary amide substrates derived from carboxylic acids could undergo a similar transformation to form medium-sized lactams under palladium catalysis. We commenced the study with the 8-aminoquinoline-coupled alanine carboxamide **5**, in the hope of forming the β-lactam product **7** [Eq. (3), Scheme 2]. The 8-aminoquinoline (AQ) group, first introduced by the Daugulis research group,[12] has demonstrated excellent ability in a number of β-C–H functionalization reactions.[13,14] Additionally, Corey and co-workers showed that β C(sp^3)–H bonds of *N*-phthaloyl-protected and AQ-coupled amino acid substrates can be readily arylated with ArI in good yield under palladium catalysis.[13a]



Scheme 1. Lactamization by the palladium-catalyzed intramolecular amination of unactivated C(sp^3)–H bonds: A) general strategy; B) previously reported approaches; C) present approach. DCE = 1,2-dichloroethene, DG = directing group.

In contrast to the facile PA-directed cyclization of **3** Val to form azetidine **4**, the reaction of AQ-coupled **5** under similar conditions with a palladium catalyst in the presence of PhI(OAc)$_2$ failed to give any of the β-lactam product **7** and provided only a trace amount of an acetoxylated side product **8**. Deuterium-exchange experiments performed on **5** revealed that its β C–H bonds were readily exchanged under similar conditions in the presence of a palladium catalyst but without PhI(OAc)$_2$ [Eq. (4), Scheme 2]. As compared with the facile coupling of the β C(sp^3)–H bonds of **5** with ArI under similar palladium catalysis at 60 °C,[12b] the oxidation of probably the same five-membered Pd^{II} palladacycle intermediate **6** with PhI(OAc)$_2$ to form Pd^{IV} was surprisingly difficult even at 110 °C.[15] The ring strain inherent in four-membered β-lactams might also have disfavored the formation of the desired product. In comparison, ring strain would not hinder the amination of the γ C(sp^3)–H bonds to form pyrrolidones. Although it is kinetically less favored, we hoped that a six-

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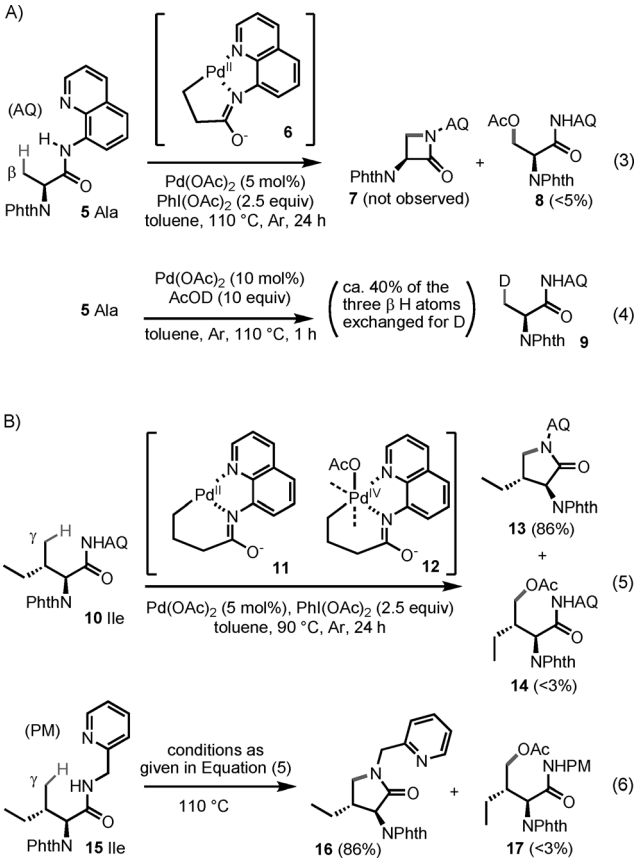
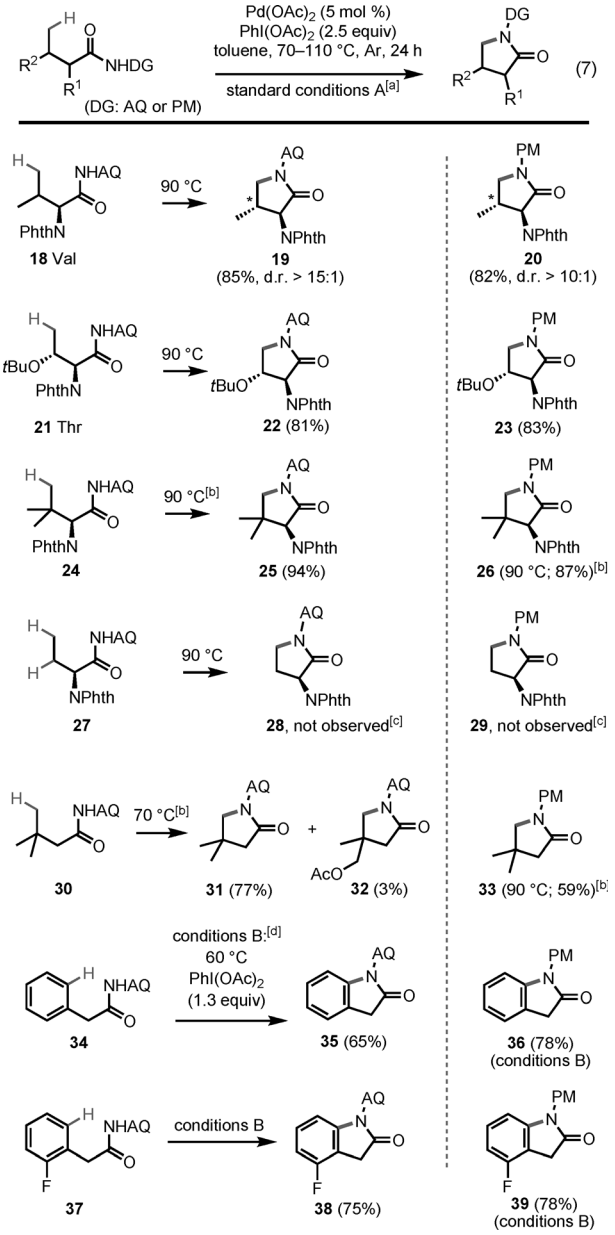


Scheme 2. Intramolecular amination of γ C(sp^3)–H bonds via A) a five-membered palladacycle and B) a six-membered palladacycle.

membered palladacycle intermediate would possess different reactivity toward $PhI(OAc)_2$-mediated oxidation. Sporadic examples reported by others as well as our own research group[16] have shown that substrates equipped with amide-linked bidentate auxiliaries can undergo reversible palladation at the γ C(sp^3)–H position to generate more remotely functionalized products.

To our delight, the cyclization of the AQ-coupled isoleucine substrate **10** proceeded cleanly under the optimized reaction conditions with $Pd(OAc)_2$ (5 mol%) and $PhI(OAc)_2$ (2.5 equiv) in toluene at 90 °C to give the γ-lactam **13** in excellent yield after 24 h, along with a trace amount of the acetoxylated product **14** [Eq. (5), Scheme 2]. Furthermore, we found that the 2-pyridylmethyl amine (PM) group, a structural analogue of AQ initially introduced by the Chatani research group for ruthenium- and nickel-catalyzed C–H functionalization reactions,[17] also enabled the same intramolecular C(sp^3)–H amination reaction in good yield at a slightly increased reaction temperature of 110 °C [Eq. (6), Scheme 2]. To the best of our knowledge, this reaction is the first synthetically useful application of the PM directing group to the palladium-catalyzed functionalization of unactivated C(sp^3)–H bonds.

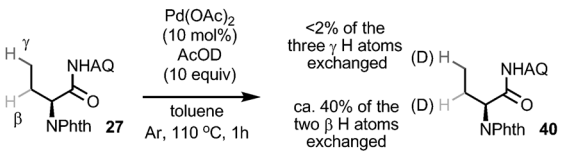
We next examined the scope of these AQ- and PM-directed lactamization reactions under the standard reaction conditions (Scheme 3). In general, butanamides bearing substituents at both α and β positions were excellent substrates, and amination of the 1° C–H bonds of their Me groups proceeded in high yield. AQ- and PM-coupled aliphatic substrates often showed comparable reactivity and selectivity. For example, *N*-Phth-protected Val substrates cyclized to form **19** and **20** in excellent yield and diastereoselectivity (d.r. > 15:1, β-Me *trans* to NPhth).[18] The *t*Bu-protected substrate **21** Thr and *tert*-butylglycine **24** cyclized



Scheme 3. Scope of the AQ- and PM-directed γ-C–H amination. All yields are for isolated products obtained from reactions on a 0.2 mmol scale; the acetoxylated side product was formed in less than 5% yield if not specified. [a] The reactions of PM substrates were carried out at 110 °C if not specified. [b] AcOH (10 equiv) was added. The reaction of **30** at 70 °C in the absence of AcOH (10 equiv) gave **31** in 69% yield and **32** in 12% yield. [c] The starting material was recovered in > 80% yield, and a mixture of monoacetoxylated products (< 10% yield) was observed by GC–MS. [d] More of the acetoxylated side product was formed at 90 °C.

well to give the corresponding lactams in above 80% yield. Intramolecular amination of the *ortho* C(sp^2)–H bonds of aryl acetamides such as **34** and **37** also occurred to provide indolinone products in good to excellent yield under further-optimized conditions in the presence of $PhI(OAc)_2$ (1.3 equiv) at 60 °C. As compared with the corresponding AQ-coupled aryl acetamides, PM-coupled substrates usually gave slightly higher cyclization yields and produced less of the acetoxylated side product (see products **35** and **36**).

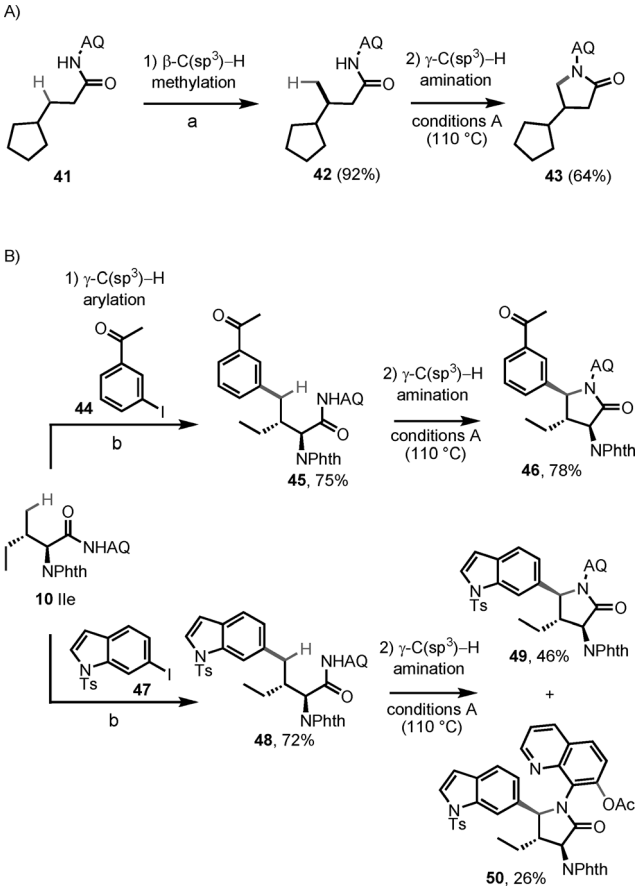
Substrate **27** without a β-Me group was much less reactive than **18** Val under the same reaction conditions (< 10% conversion); in this case, no C–N cyclized products were generated, and the acetoxylation side product was formed in less than 5% yield. Deuterium-exchange experiments performed on **27** revealed that its β-methylene C–H bonds were readily deuterated within 1 h (ca. 40%), whereas the Me group was mostly unaffected [Eq. (8)].[19] Interestingly, the



(8)

tert-butyl-substituted acetamide **30** bearing three Me groups γ to the carbonyl group and no competing β C–H bond cyclized well even at a lower temperature (70 °C) to give **31** in good yield.[20] This result indicates the relatively facile oxidation and C–N reductive elimination of the putative six-membered palladacycle intermediate. Overall, both AQ- and PM-directed intramolecular γ-C(sp^3)–H amination reactions proceeded well if the kinetic inertness of the initial γ-C–H palladation could be overcome effectively. A $Pd^{II/IV}$ catalytic manifold is most likely operative for these C–H lactamization reactions. However, the underlying mechanism that favors the C–N over the C–OAc reductive-elimination pathway is unclear.[21]

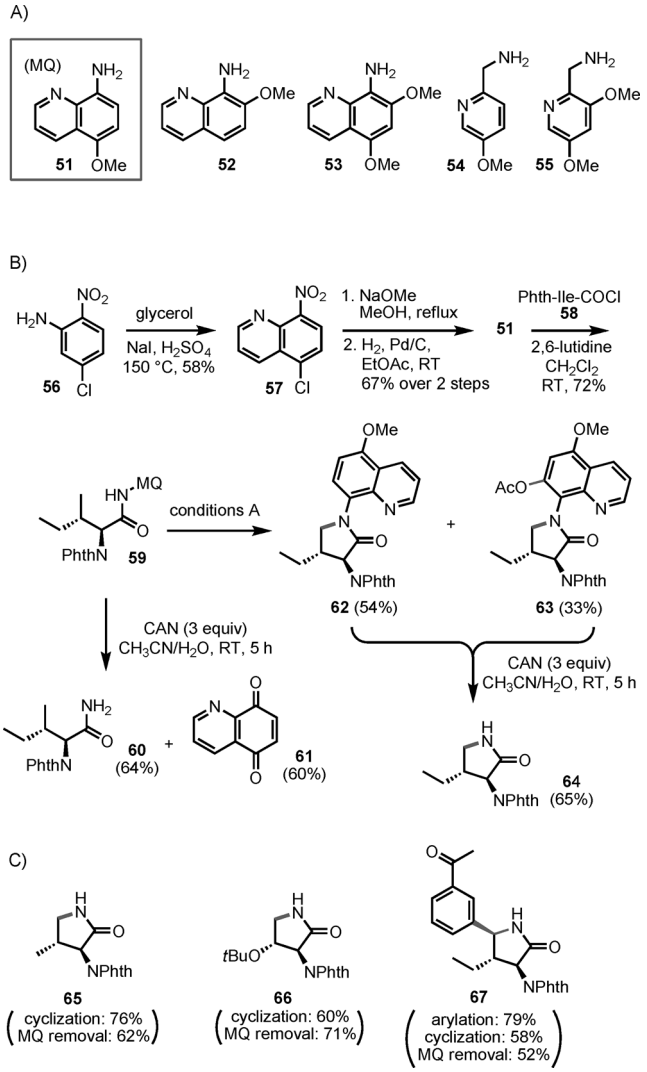
The utility of this intramolecular γ-C(sp^3)–H amination reaction can be further improved when applied in conjunction with other AQ-directed C(sp^3)–H functionalization reactions (Scheme 4). For example, substrate **41** was readily methylated at the β-methylene position with MeI (2 equiv) by our previously reported palladium-catalyzed C(sp^3)–H alkylation procedure to give **42**.[22] Compound **42** then underwent cyclization at the γ position to give **43** in moderate yield under the standard C–H amination conditions. Furthermore, β-substituted *N*-quinolylbutanamides, such as **10** Ile, can also undergo C–H monoarylation with ArI at the γ position to give γ-aryl butanamides (in this case **45** and **48**) in good yield under palladium catalysis in the presence of $(BnO)_2PO_2H$ (Scheme 4B).[23] The resulting γ-aryl butanamides can undergo intramolecular C–H amination at the 2° benzylic C–H position to form γ-arylated pyrrolidinones in good yield under the standard conditions. For example, compounds **46** and **49**, which contain three contiguous stereogenic centers, were obtained in good yield with excellent diastereoselectivity (Ar *trans* to the β substituent) from the corresponding arylated Ile precursors. Interestingly, pyrrolidone **50**, which contains an additional *ortho* acetate functionality on the AQ



Scheme 4. AQ-directed sequential C(sp^3)–H functionalization reactions involving A) β methylation and γ amination and B) γ arylation and γ amination (benzylic C–H). Reagents and conditions: a) MeI (2 equiv), $Pd(OAc)_2$ (10 mol%), AgOAc (2 equiv), $(BnO)_2PO_2H$ (20 mol%), 2-methylbutan-2-ol, 110 °C, 22 h; b) ArI (1.5 equiv), $Pd(OAc)_2$ (10 mol%), AgOAc (1.5 equiv), $(BnO)_2PO_2H$ (20 mol%), 2-methylbutan-2-ol, 110 °C, 22 h. Bn = benzyl, Ts = *p*-toluenesulfonyl.

group, was also obtained from **48**.[24] Similar acetoxylated side products were obtained in less than 5% yield for substrates bearing an electron-deficient γ arene group (e.g. **45**).

Finally, we addressed the last critical issue regarding this intramolecular C–H lactamization method: removal of the auxiliary group. Cleavage of the Ar–N bond under mild conditions is inherently difficult and has long restricted the synthetic utility of many auxiliary-mediated C–H functionalization reactions. Inspired by the *para*-methoxyphenyl (PMP) protecting group for amines, we envisioned that the installation of a methoxy group at the *para* and/or *ortho* positions of the parent auxiliary groups could enable their removal with ceric ammonium nitrate (CAN) under mild conditions.[25] Among the five modified auxiliary groups tested (Scheme 5A), 8-amino-5-methoxyquinoline (MQ, **51**) performed best in both cyclization and deprotection steps. Compound **51** can be readily prepared in three steps from the commercially available aniline precursor **56** through a sequence involving a Skraup reaction, S_NAr substitution with NaOMe, and reduction of the NO_2 group to NH_2.[26] The MQ group could be installed readily on carboxylic acid substrates through



Scheme 5. Identification, synthesis, and application of the readily removable MQ auxiliary group: A) modified AQ and PM auxiliaries; B) synthesis and test reactions with the MQ auxiliary group; C) selected applications of the MQ auxiliary.

standard amide-coupling methods. To our delight, removal of the MQ group of **59** Ile proceeded smoothly in the presence of CAN (3 equiv) in CH_3CN/H_2O at room temperature for 5 h to give the primary-amide product **60** in good yield along with the quinone by-product **61**. The palladium-catalyzed intramolecular C–H amination reaction of **59** under conditions A at 110 °C gave a 5:3 mixture of the cyclized product **62** and an acetoxylated compound **63** in excellent combined yield.[27] Treatment of the mixture of **62** and **63** with CAN (3 equiv) in CH_3CN/H_2O at room temperature gave the free pyrrolidone **64** in 65 % yield.[28] Pyrrolidones **65**–**67**[29] were also obtained in good yield with excellent diastereoselectivity by MQ-facilitated C–H arylation, C–H lactamization, and the CAN-mediated removal of MQ (Scheme 5C). Compound **51** is now commercially available (Sigma-Aldrich). In comparison, the use of 7-methoxy-8-aminoquinoline (**52**) led to a poor cyclization yield, although the removal of this auxiliary under the same conditions with CAN proceeded well. 2-(3-Methoxypyridyl)methyl amine (**54**) promoted the C–H lactamization reaction in good yield but could not be removed by treatment with CAN.

In summary, we have developed a new set of reactions for the synthesis of pyrrolidones and indolinones by the palladium-catalyzed carboxamide-directed intramolecular amination of unactivated C(sp^3)–H and C(sp^2)–H bonds at the γ position of secondary-amide precursors. These reactions harness the unique redox reactivity of six-membered palladacycle intermediates, which are kinetically less favorable than five-membered palladacycles but react readily with PhI(OAc)$_2$ to give γ-lactam products with high selectivity. These lactamization reactions are efficient, versatile, and require inexpensive reagents. They can be applied along with other palladium-catalyzed C(sp^3)–H functionalization reactions in a sequential manner to quickly transform readily accessible carboxylic acid starting materials into diverse pyrrolidinone products with complex substitution patterns. Finally, we have introduced the MQ auxiliary, which can be removed readily and greatly improves the synthetic utility of these reactions by enabling applications in the synthesis of complex molecules.

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[18] A five-membered palladacycle with the *N*-Phth and β Me groups in a *trans* configuration is most likely responsible for the observed diastereoselectivity.

[19] Deuteration at the γ position (>10%) occurred during an extended reaction time (20 h).

[20] The addition of AcOH (10 equiv) was found to be beneficial in suppressing the formation of the acetoxylated cyclized side product **32**.

[21] Preference for C–N reductive elimination to form cyclized azetidine products was observed for β-substituted substrates in the palladium-catalyzed PA-directed intramolecular $C(sp^3)$–H amination (Ref. [9a]). The substitution pattern of the AQ-coupled carboxamide substrates also has a notable impact on their reactivity in this palladium-catalyzed C–H lactamization reaction.

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[26] Compound **51** was prepared on the basis of a reported procedure under modified conditions; see: Medina Padilla et al., Patent WO2010066832, June 23, **2011**.

[27] Control experiments showed that compound **62** cannot be converted into **63** under these conditions of palladium catalysis in the presence of $PhI(OAc)_2$.

[28] Both compounds can be readily deprotected with CAN in good yield. Compounds **62** and **63** have slightly different TLC R_f values (by ca. 0.1) on silica gel. They can be separated by flash chromatography for structural characterization. They can also be conveniently collected together during the purification step and subjected to deprotection as a mixture. A similar TLC pattern was observed during the preparation of compounds **65** and **66**.

[29] Only a trace amount of the *ortho*-acetoxylated side product was observed during the intramolecular C–H amination of the MQ-coupled precursor of **67**, possibly owing to the electron-deficient nature of the aryl group. The same reactivity was observed in the formation of AQ-coupled **46**.

