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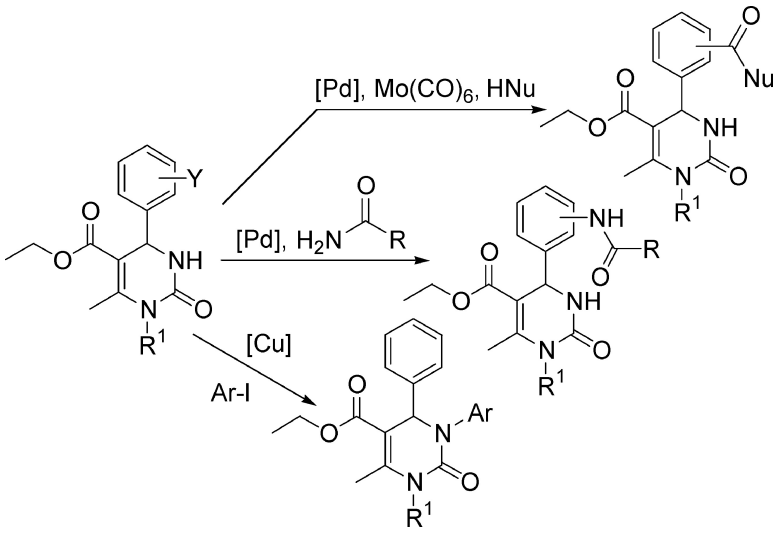

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Microwave-Enhanced and Metal-Catalyzed Functionalizations of the 4-Aryl-Dihydropyrimidone Template

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Progress in organometallic catalysis and recent advancements in the development of carbonylative reaction protocols without direct use of carbon monoxide have been utilized for efficient functionalizations of 4-aryl-dihydropyrimidone structures. The use of modern microwave technology enabled both high reaction rates and convenient handling. Examples of palladium-catalyzed cross-couplings, Heck reactions, amino- and alkoxycarbonylations, and direct N-amidations of 4-(bromophenyl)-dihydropyrimidones were performed. Further, the first N3-arylations of the dihydropyrimidone ring system were successfully completed using the copper-catalyzed Goldberg reaction. Altogether, these protocols provide new tools for rapid generation of novel and diverse dihydropyrimidone derivatives.

Introduction

The development of high-throughput synthesis continues to be a key objective within the drug discovery industry.[1] In modern laboratories, organic transformations must be rapidly executed and products readily purified. Clearly, there will be a continuing need for the definition of novel reaction routes to both multifunctional scaffolds for lead generation and to unique druglike heterocyclic structures. In this field, controlled microwave irradiation has proved to be a powerful tool for both speeding up chemical optimizations and for efficient preparation of new target compounds.[2−5] The recent developments in highly chemoselective metal-catalyzed coupling reactions have further enabled direct incorporation of a wide variety of chemical functionalities that previously were difficult to accomplish.[6] However, the sometimes tedious pinpointing of the appropriate reaction components, together with the long reaction times frequently required for full conversions, have limited the exploitation of these protocols in many high-throughput and diversity-oriented efforts. Therefore, the synthetic expedience of rapid microwave superheating might be of special value for decorating privileged heterocyclic structures using metal-catalyzed transformations.[7]

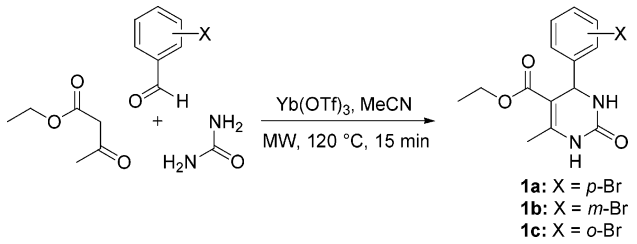
Derivatives of dihydropyrimidones (DHPMs) have widespread pharmacological activities, and they are classified as one of the most important groups of druglike scaffolds.[8] Because of the pharmaceutical interest and the convenient access to various dihydropyrimidones by the Biginelli multicomponent reaction,[9,10] we selected this privileged core as a model system for exemplifying our diversity strategy. Thus, ultimately, we aim to develop orthogonal protocols for direct installation of a large number of functionalities at any given position of the DHPM template.[11−14]

In this article, we present the successful application of not only standard cross-couplings and Heck reactions but also relatively unexplored carbonylative in situ protocols and two different types of N-arylation of amide-type nitrogens for the high-speed preparation of small collections of novel DHPM compounds. Ortho-, meta- and para-substituted 4-bromoaryl-DHPMs were chosen as arylpalladium precursors, while nonhalogen containing 4-aryl-DHPMs were utilized as nitrogen nucleophiles in complementary Goldberg couplings.[15−17] In addition, a novel intramolecular endocyclic Heck reaction will be presented. All transformations were performed using sealed reaction vessels and controlled microwave heating.

Results and Discussion

Preparation of 4-(Bromophenyl)-DHPMs. The bromophenyl-substituted DHPMs **1a**−**c** were prepared in close analogy to our previously described microwave-assisted Biginelli multicomponent condensations in both small-[18] and large-scale[19] reactions, utilizing single- and multimode microwave reactors, respectively (Scheme 1). Fine-tuning

Scheme 1. Synthesis of 4-(Bromophenyl)-DHPMs



1a: X = *p*-Br
1b: X = *m*-Br
1c: X = *o*-Br

of the published protocols was first performed in a single-mode reactor on a 1-mmol scale. Conducting the Biginelli

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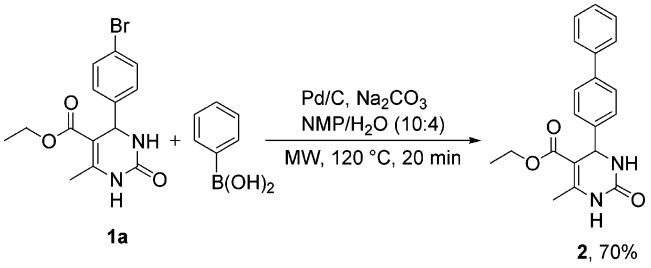
reaction with 1.5 equiv of ethyl acetoacetate, 1 equiv of urea, 1 equiv of *o*-, *m*-, and *p*-bromobenzaldehyde, respectively, and 10 mol % of $Yb(OTf)_3$ as catalyst in MeCN at 120 °C for 15 min under microwave irradiation gave the best results. A direct scale-up of these conditions to 40 mmol allowed the individual preparation of all three required building blocks **1a**−**c** in one single irradiation process utilizing a multivessel microwave system. As previously reported, both reaction time and temperature could be directly transferred from the single-mode to the multimode platform, providing nearly identical product yields (73−85% of **1a**−**c** in 1-mmol scale and 65−76% in 40-mmol scale, Scheme 1).[19]

Palladium-Catalyzed C−C Couplings of 4-(Bromophenyl)-DHPMs. To investigate the general usefulness of **1a**−**c** in palladium(0)-catalyzed reactions, we decided to apply standard type C−C coupling reactions onto the 4-(bromophenyl)-DHPM core using high-density microwave heating.

As an example of a Pd(0)-catalyzed cross-coupling reaction, a Suzuki coupling was executed under 15 min of microwave irradition. Slightly surprising, the reaction of aryl bromide **1a** and phenylboronic acid, yielding the 4-(bisaryl)-DHPM, was best performed under heterogeneous catalysis utilizing inexpensive 5% Pd/C (Scheme 2).[20,21] This type of

Scheme 2. Suzuki Coupling of 4-(*p*-Bromophenyl)-DHPM with Phenylboronic Acid

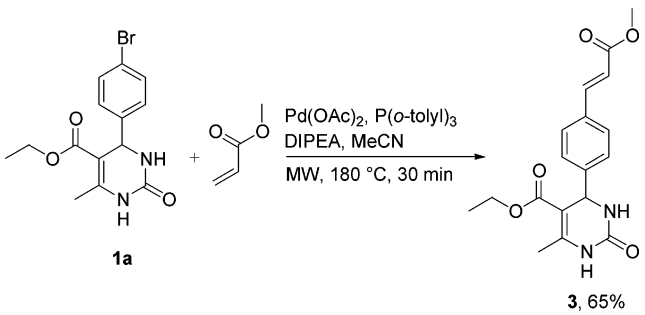


catalyst showed superior results compared to the homogeneous precatalyst $Pd(PPh_3)_2Cl_2$. By switching from K_2CO_3 to Na_2CO_3 as base, almost complete conversion of **1a** was observed. Applying the improved reaction conditions in a 0.5-mmol scale, with 0.4 mol % of Pd/C, 2 equiv of Na_2CO_3, and 1.2 equiv of phenylboronic acid in NMP/H_2O at 120 °C for 20 min, biphenyl **2** was obtained in 70% isolated yield. Gratifyingly, scaffold **1a** was thus found to react as anticipated, proving to be a useful substrate in Pd(0) chemistry.

In a second evaluation example, 4-(*p*-bromophenyl)-DHPM **1a** was reacted with methyl acrylate under microwave heating in an intermolecular Heck reaction (Scheme 3).[22] After some modifications of the catalytic system and by employing different bases and solvents, the best result, 65% isolated yield of **3**, was obtained by conducting the 0.5-mmol scale reaction with 2 mol % of $Pd(OAc)_2$, 4 mol % of tri(*o*-tolyl)phosphine, and 1 equiv of *N*,*N*-diisopropylethylamine (DIPEA) in MeCN at 180 °C for 30 min.

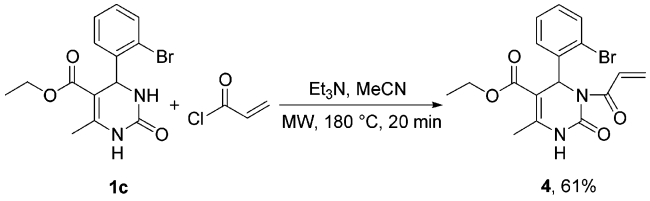
Intramolecular Heck Cyclization. Novel methods for rigidification of privileged structures, such as DHPMs, are always of interest in medicinal chemistry projects due to the possibility of gaining information regarding the bioactive conformation.[23] In addition, the intramolecular Heck reaction

Scheme 3. Heck Coupling of 4-(*p*-Bromophenyl)-DHPM with Methyl Acrylate



is well-established for the construction of polycyclic ring systems.[24,25] Inspired by this knowledge and the successful intermolecular Heck reaction described earlier, we therefore decided to attempt to connect the 4-aryl group and the dihydropyrimidone ring using an envisioned endo-cyclic Heck reaction, delivering a fused benzoazepine−DHPM system after a formal trans palladium(II) β-hydride elimination. The starting material for the intramolecular Heck reaction, DHPM **4**, was prepared by selective N3-acylation of 4-(*o*-bromophenyl)-dihydropyrimidone **1c** with acryloyl chloride (Scheme 4). Adapting our previously reported

Scheme 4. N3-Acylation of 4-(*o*-Bromophenyl)-DHPM with Acryloyl Chloride

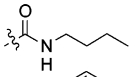
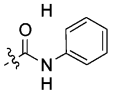
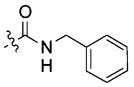
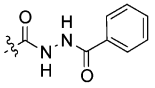
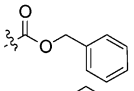
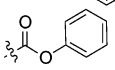
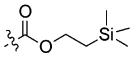


microwave-assisted acylation method,[26] reaction of **1a** with acryloyl chloride in MeCN in the presence of triethylamine as a base (180 °C, 20 min), followed by filtration of the crude reaction mixture through a SPE cartridge filled with a basic Al_2O_3/K_2CO_3 mixture to retain the excess acid chloride, provided the desired DHPM **4** in 61% isolated yield (Scheme 4).

Using classical Heck-coupling conditions,[22] a small-scale temperature/time optimization study was commenced. It was quickly realized that complete ring closure could be obtained by heating olefin **4**, 5 mol % of Herrmann's palladacycle[27] ($Pd_2(OAc)_2[P(o\text{-tolyl})_3]_2$) and 3 equiv of DIPEA in DMF/H_2O or MeCN/H_2O at 150 °C for 15 min. The test reactions were subsequently pooled together, and a compound with the expected molecular weight was isolated by preparative LC/MS. Standard ^1H NMR analysis proved the structure of the endo-cyclization product **5** ($J_{(\text{vinylic H−H})}$ = 12.2 Hz). Running a single reaction at increased scale (0.20 mmol) with the aqueous MeCN conditions mentioned above, a yield of 78% of **5** was isolated after flash chromatography (Scheme 5).

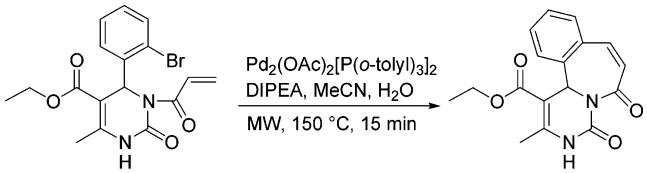
To gain more information regarding the preferred low-energy conformation, a high-level density functional theory (DFT) calculation (B3LYP/6-31G*) on the geometry of the internal Heck product **5** was conducted. In contrast to our expectations, the computational experiment revealed that

Table 1. Preparative Results for Palladium-Catalyzed Carbonylations of 4-(Bromophenyl)-DHPMs Using $Mo(CO)_6$ as the CO Source

Ar-Br	NuH (equiv)	Temp (°C)		Product	Yield (%)[a]
1a	*n*-Butylamine (3)	130	*p*- 	**6a**	87
1a	Aniline (3)	130	*p*- 	**6b**	83
1a	Benzylamine (3)	130	*p*- 	**6c**	78
1b			*m*-	**6d**	65
1a	Morpholine (3)	140	*p*- 	**6e**	56
1b			*m*-	**6f**	71
1c			*o*-	**6g**	21
1a	Benzhydrazide (3)	130	*p*- 	**6h**	35[b]
1a	Methanol (solvent)	110	*p*- 	**6i**	77
1b			*m*-	**6j**	71
1c		120	*o*-	**6k**	24
1a	Benzyl alcohol (5)	140	*p*- 	**6l**	45
1a	Phenol (5)	140	*p*- 	**6m**	42
1a	2-TMS-ethanol (5)	140	*p*- 	**6n**	52

[a] Isolated yields after chromatographic purification (>95% purity by ^{1}H NMR). [b] Reaction time reduced to 5 min.

Scheme 5. Intramolecular Seven-Membered Heck Endo-Cyclization



4 **5**, 78%

the formation of a tricyclic ring system did not flatten out the overall geometry. On the contrary, the aryl ring was still locked in a pseudoaxial position, resembling other nonfused 4-aryl-dihydropyrimidines.[28,29] In fact, here, the intramolecular Heck strategy allows locking of the aryl ring in the proposed bioactive, that is, the pseudoaxial, orientation.[30]

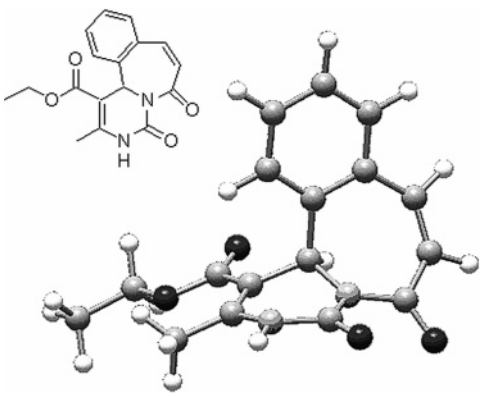
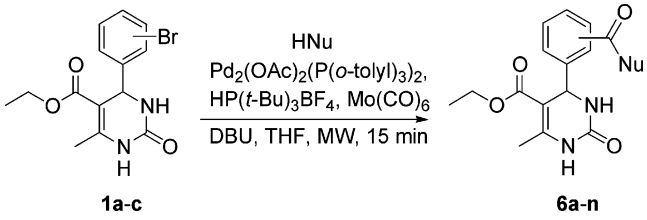


Figure 1. Optimized geometry of rigidified **5** (B3LYP/6-31G*)

In Situ Carbonylations of 4-(Bromophenyl)-DHPMs. Carbonylation chemistry has been extensively used in organic synthesis because of its unique possibilities and great versatility.[31] The use of carbonylative methods in standard laboratories have, however, been hampered by the emergency of increased safety regulations regarding handling, transport, and storage of toxic, gaseous carbon monoxide.[32] Therefore, we are currently engaged in a research program aiming at developing and identifying alternative liquid or solid CO sources.[32,33] Previously, we have published methods for microwave-heated aminocarbonylations,[34,35] alkoxycarbonylations,[36] and hydrazidocarbonylations,[37] enabling smooth substitution of aromatic halides for amides, esters and *N*,*N*′-diacylhydrazines, exploiting molybdenum hexacarbonyl as a reliable CO-releasing solid reagent. In this proof-of-concept study, we expand the scope of these palladium(0)-catalyzed transformations to produce functionalized DHPM derivatives employing different nucleophiles (HNu).

With aryl bromides **1a**−**c** in hand, we first explored the robust aminocarbonylations following our published noninert molybdenum hexacarbonyl-based method.[35] Although our standard aminocarbonylation protocol for aryl bromides using Herrmann's palladacycle was performing well also with this scaffold, an addition of Fu's salt ($HP(t\text{-}Bu)_3BF_4$)[38] according to the reported hydrazidocarbonylation protocol[37] allowed a reduction in reaction temperature (in most cases, from 150 to 130 °C, Scheme 6). Unfortunately, with simpler palladium sources than the palladacycle, such as $Pd(OAc)_2$ or $Pd_2(dba)_3$, full conversion of **1** could not be reached, even if combined with Fu's salt.

Scheme 6. Carbonylation Reactions Using $Mo(CO)_6$ as the CO Source



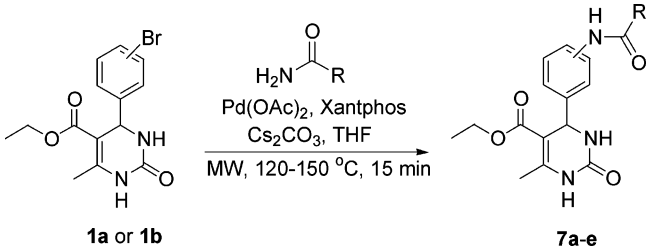
The preparative reactions were carried out in 0.15-mmol scale using 15 min of controlled microwave heating. As expected, good to excellent yields of amides **6a**−**f** were isolated with both para- and meta-substituted **1a** and **1b** (56−87%, Table 1). Aminocarbonylation of **1c** with morpholine produced only low amounts of the *ortho*-amide product **6g** together with a range of byproducts. Employing benzhydrazide as nucleophile afforded the diacylhydrazine **6h** in only 5 min but partial product decomposition under these conditions and difficulties in the purification allowed only a moderate 35% yield.

The next part of our study concerned alkoxycarbonylation reactions, providing ester-protected acids **6i**−**n**. Rewardingly, by adding the Fu salt and by replacing THF with methanol as a combined nucleophile and solvent, *para* and *meta* methyl esters **6i** and **6j** were obtained in good yields (71−77%) at temperatures as low as 110 °C. In accordance with the sluggish aminocarbonylation of **1c**, the corresponding reaction with methanol produced only poor yields of *ortho* methyl ester **6k**. In both of these instances, debrominated starting material was the main product, as detected by LC/MS of the reaction mixtures. Alkoxycarbonylation of **1a** using only 5 equiv of benzyl alcohol, phenol, and 2-(trimethylsilyl)-ethanol, respectively, furnished esters **6l**−**n** in moderate 42−52% yields.

Amide N-Arylation Reactions. In the 1990s, a plethora of methods for arylations of nucleophilic amines were developed.[39] However, the corresponding palladium- or copper-catalyzed N-arylation of amides have gained an increased interest only in the past few years.[16,17,40] In contrast to relatively mild palladium-Xantphos-catalyzed amidation reactions, the copper-catalyzed N-arylation of amides with aromatic halides (the Goldberg reaction) typically requires drastic reaction conditions, such as heating to temperatures above 200 °C for several hours, and commonly leads to only moderate productivity. In some instances, by employing an additional ligand[41−43] or using aryl boronic acids[44−46] instead of aryl halides as arylating agents, reaction temperatures were decreased to below 130 °C with concomitant increase in product yields.

From a diversity-targeting perspective, we were interested in preparing the inverse amide analogues to the aminocarbonylation products **6a**−**d**. To accomplish this, we decided to explore the scope of the palladium-catalyzed version of the amide N-arylation reaction. By slightly modifying the conditions reported by Yin and Buchwald[40] a successful microwave protocol was developed. Benzamide and acetamide could be cleanly N-arylated using **1a** or **1b** with $Pd(OAc)_2$ as the Pd source, Xantphos as the ligand, and cesium carbonate as the base in dry THF, delivering products **7a**−**d**

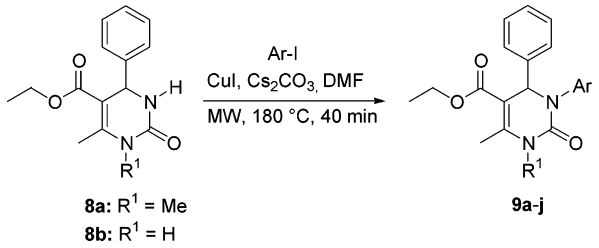
Scheme 7. Palladium-Catalyzed N-Amidations of 4-(Bromophenyl)-DHPMs



in 72−88% yield (Scheme 7). The reaction temperatures were varied to deliver full conversion of starting aryl bromides **1a** and **1b** in less than 15 min of microwave irradiation. The selected reaction protocol could also be used to couple *tert*-butylcarbamate with **1a** to afford the boc-protected aniline derivative **7e** in 62% yield, employing an only slightly higher reaction temperature (150 °C).

Direct N3-Arylations of DHPMs. To the best of our knowledge, the N3-arylation of DHPMs **8** with either aryl halides or boronic acids has not been reported (Scheme 8),

Scheme 8. N3-Arylation of DHPMs via the Goldberg Reaction.



and a search in the SciFinder Scholar database revealed that among the more than 10 000 DHPM entries, no examples of N3-arylated analogues exist. It should be noted that N3-arylated DHPM analogues cannot be obtained by classical Biginelli condensation strategies involving *N*-arylureas. Here, the corresponding N1-substituted derivates will be formed exclusively.[47,48] To introduce novel diversity in the N3-position of the DHPM scaffold, we first attempted to carry out palladium-catalyzed N3-arylations. Disappointingly, the protocol presented in Scheme 7 for amidation of 4-bromophenyl-DHPMs provided no product in the attempted N3-arylations of N1-blocked **8a** using aryl iodides.[40,49] Lange and co-workers have recently demonstrated that by utilizing high-temperature microwave heating, the copper-catalyzed Goldberg reaction could be accelerated from several hours down to 20−40 min using only very small amounts of solvent (2 mol equiv).[50] Thus inspired by this achievement, we decided to investigate this procedure for the desired N3-arylations. In the process of selecting suitable reaction conditions for the N3-arylation of the two model DHPMs **8a** and **8b**,[18] different bases, solvents, and reaction conditions were screened.

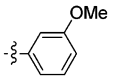
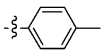
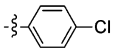
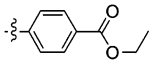
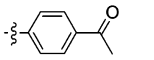
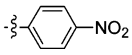
The most general Goldberg protocol identified used a concentrated mixture of 20 mol % of CuI as catalyst, 1.5 equiv of Cs_2CO_3 as base, and 5 mol equiv of DMF as solvent (Scheme 8, Table 3). The reactions were conducted at 180 °C for 40 min with a set of eight differently substituted aryl iodides. Performing the reaction at lower temperatures for

Table 2. Preparative Results for Palladium-Catalyzed N-Amidation of 4-(Bromophenyl)-DHPMs

Ar-X	Reagent	Temp (°C)		Product	Yield (%)[a]
1a	Acetamide	140	*p*-	**7a**	85
1b	Acetamide	140	*m*-	**7b**	79
1a	Benzamide	120	*p*-	**7c**	72
1b	Benzamide	120	*m*-	**7d**	88
1a	*tert*-Butyl-carbamate	150	*p*-	**7e**	62

[a] Isolated yields after flash chromatographic purification (>95% purity by ^{1}H NMR).

Table 3. Preparative Results for Goldberg N3-arylation of DHPMs with Aryl Iodides

Starting material	R_1	-Ar	Product	Yield (%)[a]
8a	Me		**9a**	63
8a	Me		**9b**	34
8a	Me		**9c**	69
8b	H		**9d**	36
8a	Me		**9e**	70
8a	Me		**9f**	83
8a	Me		**9g**	80
8b	H		**9h**	13
8a	Me		**9i**	67
8a	Me		**9j**	49

[a] Yields refer to isolated yields after flash chromatographic purification (>97% purity by HPLC analysis at 215 nm).

the same or prolonged reaction time resulted in lower conversion. On the other hand, by carrying out the reaction at higher temperatures, the conversion could not be further improved, and more impurities were detected, probably due to the decomposition of DMF.[33]

After automated flash chromatography, the desired *N*3-aryl-DHPMs **9a**−**j** were obtained in low to excellent isolated yields (13−83%, see Table 3). It should be pointed out that N1-methylated DHPMs gave distinctly better yields than the unsubstituted product analogues **9d** and **9h**, although no isomeric N1-arylated derivates were isolated. We assume that the presence of the enamine moiety (O═C−C═C−NH) in the DHPM scaffold results in a decreased nucleophilicity/reactivity of the N1 over the N3 amide nitrogen,[14] therefore allowing a selective N3-arylation.

The substitution pattern of the aryl iodide had only little effect on the isolated product yields, as can be seen by, for example, comparing esters **9f** and **9g**, affording 83 and 80% yields (Table 3), respectively. Despite the steric hindrance of the ortho substituent, the yield was as high as for the corresponding para-substituted substrate. Electron-poor aryl iodides tended to give somewhat better yields than electron-rich aryl iodides, except for the case of the highly reactive 1-iodo-4-nitrobenzene, which showed a comparatively lower yield of product **9j** (49%) due to concomitant reduction of the nitro group.

Not surprisingly, attempts to use aryl bromides or chlorides in the Goldberg reaction with either DHPM **8a** or **8b** met with little success. While no conversion was observed with aryl chlorides, activated 1-bromo-4-nitrobenzene showed some degree of conversion by HPLC monitoring but led to only low yields of isolated product after chromatographic purification. Variations of the Goldberg reaction conditions, for example, using *N*,*N*′-dimethyl ethylenediamine as ligand, did not lead to any improvements on the reaction.[41,43,51]

Conclusions

We have developed a number of fast methods for transition-metal-catalyzed decoration of 4-aryl-dihydropyrimidones using controlled microwave heating as the energy source. The palladium-catalyzed protocols allow facile installation of diversities into 4-(bromoaryl)-DHPMs. It should be mentioned that both in situ carbonylations using different nitrogen and oxygen nucleophiles and direct N-arylations efficiently generated functionalized amides or esters after only short periods of high-density microwave heating. Perhaps of greater importance, a new class of N3-arylated DHPMs was prepared by copper-catalyzed Goldberg arylations. These compounds are not available from classical Biginelli-type condensations, although 40 min of microwave heating conveniently delivers these products from N1-methylated starting materials. Combined, the presented methodologies will facilitate future high-speed generations of large arrays of novel structures. Given the interest in privileged DHPM-based compound selections, this strategy should find applications in different areas of drug discovery.

Experimental Section

General. The large-scale microwave synthesis of compounds **1a**−**c** was carried out in a Synthos 3000 multimode batch reactor from Anton Paar GmbH (Graz).[19] All other microwave-assisted synthesis was carried out in a Smith/Emrys Synthesizer single-mode microwave cavity producing controlled irradiation at 2450 MHz (Biotage AB, Uppsala).[14] TLC analysis was performed on precoated Silica gel 60 F_{254}

plates (E. Merck). Flash column chromatography was performed using Merck Silica gel 60 or 60 RP-18 (0.040−0.063 mm). The purification of the products of the N3-aryl DHPM library was performed with an automated Biotage SP4 flash chromatography system. RP-HPLC was used for reaction monitoring and purity control. Low-resolution mass spectra were obtained from a Hewlett-Packard LC/MSD 1100 series instrument in the atmospheric pressure chemical ionization (positive APCI) mode. ^{1}H NMR spectra were recorded at 360 or 400 MHz as indicated, and ^{13}C NMR spectra were recorded at 100.5 MHz. THF was freshly distilled over Na/benzophenone. Starting materials **1a**−**c**[52−54] and **8a**,**b**[18] are known compounds. The heterogeneous palladium catalyst (E 105 CA/W 5%, batch P1/2521) consisted of 5% palladium on active charcoal, contained 56.8% H_2O, and was obtained from Degussa AG, Hanau, Germany.[21]

Preparation of 4-(Bromophenyl)-dihydropyrimidones 1a−c. 1. Small-Scale. A mixture of the appropriate bromobenzaldehyde (1.0 mmol, 185 mg), urea (1.0 mmol, 60 mg), ethyl acetoacetate (1.5 mmol, 195 mg, 191 μL), and $Yb(OTf)_3$ (0.1 mmol, 62 mg) in MeCN (0.5 mL) was irradiated at 120 °C for 15 min in a 2-mL microwave vial. After cooling to room temperature, the vial was kept at 4 °C overnight. After adding 1 g of ice, the precipitate was filtered off, washed with cold H_2O/EtOH 1:1, and dried at 70 °C to give the known DHPMs **1a** (77%), **1b** (85%), and **1c** (73%) in 95% purity (HPLC at 215 nm).

2. Scale-Up. Three 80-mL quartz reaction vessels equipped with Teflon-coated stirring bars (2.5 cm) were individually charged with urea (40 mmol, 2.40 g) and $Yb(OTf)_3$ (4.0 mmol, 2.48 g). To each of these vessels was added MeCN (20 mL) followed by stirring at room temperature for approximately 10−15 min to enable the starting materials to dissolve. Subsequently, the appropriate bromobenzaldehyde (40 mmol, 7.40 g) and ethyl acetoacetate (60 mmol, 7.81 g, 7.65 mL) were added. Into the fourth (dummy) quartz vessel, only 20 mL of MeCN was charged. The reaction vessels were sealed and inserted into the eight-position rotor. The reaction mixtures were heated to 120 °C employing a 3-min linear heating ramp and then irradiated for an additional 15 min at 120 °C. After cooling to 40 °C by an air flow (∼20 min), individual vessels were removed from the rotor and kept at 4 °C overnight. After addition of 40 g of ice, the precipitates were filtered by suction and washed with cold H_2O/EtOH 1:1 and dried at 70 °C to provide DHPMs **1a** (68%), **1b** (76%), and **1c** (65%) in >95% purity (HPLC at 215 nm).

1a. ^{1}H NMR (DMSO-d_6, 360 MHz): δ 1.09 (t, J = 7.1 Hz, 3H), 2.24 (s, 3H), 3.98 (q, J = 7.1 Hz, 2H), 5.12 (d, J = 2.3 Hz, 1H), 7.18 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.3 Hz, 2H), 7.77 (br s, 1H), 9.25 (br s, 1H); mp 200−204 °C (lit. mp 197 °C).[52]

1b. ^{1}H NMR (DMSO-d_6, 360 MHz): δ 1.10 (t, J = 7.1 Hz, 3H), 2.25 (s, 3H), 3.94−4.04 (m, 2H), 5.14 (d, J = 3.1 Hz, 1H), 7.23 (d, J = 7.7 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 7.38 (br s, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.80 (br s, 1H); mp 184−186 °C (lit. mp 185−186 °C).[53]

1c. ^{1}H NMR (DMSO-d_6, 360 MHz): δ 0.99 (t, J = 7.1 Hz, 3H), 2.30 (s, 3H), 3.89 (q, J = 7.0 Hz, 2H), 5.60 (d, J = 2.3 Hz, 1H), 7.16−7.21 (m, 1H), 7.29−7.38 (m, 2H), 7.56 (d, J = 7.9 Hz, 1H), 7.70 (br s, 1H), 9.28 (br s, 1H); mp 206−207 °C (lit. mp 206−208 °C).[54]

Suzuki-Coupling of 4-(*p*-Bromophenyl)-DHPM with Phenylboronic Acid. A mixture of 4-(*p*-bromophenyl)-DHPM **1a** (0.5 mmol, 170 mg), phenylboronic acid (0.6 mmol, 73 mg), Na_2CO_3 (1.0 mmol, 106 mg), and Pd/C[21] (2 μmol, 4.5 mg) in NMP/H_2O 10:4 (1.5 mL) was irradiated at 120 °C for 20 min in a 2-mL microwave vial. After cooling, ice water was added to the reaction mixture, and the formed precipitate was filtered off, washed with water, and dried at 50 °C. Subsequently, the precipitate was dissolved in $CHCl_3$, the catalyst was filtered off, and the solvent was evaporated. The residue was dried at 50 °C overnight under vacuum, and DHPM **2** was obtained as a yellow-white solid in 70% yield (118 mg).

2. ^{1}H NMR ($CDCl_3$, 360 MHz): δ 1.21 (t, J = 7.1 Hz, 3H), 2.40 (s, 3H), 4.12 (q, J = 7.0 Hz, 2H), 5.48 (s, 1H), 7.27−7.58 (m, 11H). MS (pos. APCI): 337.5 (M + 1). Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.14; H, 5.97; N, 8.10. mp 232−235 °C.

Heck-Coupling of 4-(*p*-Bromophenyl)-DHPM with Methyl Acrylate. A mixture of $Pd(OAc)_2$ (0.01 mmol, 2 mg), tri(*o*-tolyl)phosphine (0.02 mmol, 7 mg), and DIPEA (*N*,*N*-diisopropylethylamine) (0.5 mmol, 65 mg, 88 μL) was stirred in MeCN (3 mL) at 60 °C for 45 min. Subsequently, 4-(*p*-bromophenyl)-DHPM **1a** (0.5 mmol, 170 mg) and methyl acrylate (0.5 mmol, 43 mg, 45 μL) were added, and the reaction mixture was irradiated at 180 °C for 30 min in a 2-mL microwave vial. After cooling, 15 mL of H_2O was added, and the mixture was stirred and further cooled on an ice bath for 1 h. The precipitate was filtered off and dissolved in 20 mL of CH_2Cl_2. A second filtration removed the precipitated palladium catalyst, and the solvent was evaporated. The product, DHPM **3**, was obtained after drying at 50 °C under vacuum as a yellowish solid in 65% yield (112 mg).

3. ^{1}H NMR ($CDCl_3$, 360 MHz): δ 1.19 (t, J = 7.1 Hz, 3H), 2.37 (s, 3H), 3.82 (s, 3H), 4.10 (q, J = 7.0 Hz, 2H), 5.43 (s, 1H), 6.43 (d, J = 16.0 MHz, 1H), 7.27−7.50 (m, 6H), 7.67 (d, J = 16.0 MHz, 1H). MS (pos. APCI): 345.0 (M + 1). Anal. Calcd for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.85; N, 8.13. Found: C, 62.59; H, 5.80; N, 7.45. mp 112−115 °C.

Acylation of 4-(*o*-Bromophenyl)-DHPM at the N3-Position with Acryloyl Chloride. A mixture of DHPM **1c** (0.25 mmol, 85 mg), acryloyl chloride (0.625 mmol, 57 mg, 51 μL), and Et_3N (0.375 mmol, 38 mg, 53 μL) in MeCN (0.5 mL) was irradiated in a 2-mL microwave vial at 180 °C for 20 min. After cooling to room temperature, the reaction mixture was filtered through a SPE cartridge (60 × 12 mm i.d.) filled with 1 cm of basic Al_2O_3/K_2CO_3 2:1, and the product was thereafter eluted with 5 mL of EtOAc. The filtrate was evaporated, and the residue was titurated with Et_2O to obtain DHPM **4** as a yellow solid in 62% yield (61 mg) and 96% purity (HPLC at 215 nm).

4. ^{1}H NMR ($CDCl_3$, 360 MHz): δ 1.26 (t, J = 7.1 Hz, 3H), 2.40 (s, 3H), 4.13−4.24 (m, 2H), 5.73−5.76 (m, 1H), 6.37−6.42 (m, 1H), 6.69 (s, 1H), 7.04−7.14 (m, 2H), 7.23−

7.25 (m, 1H), 7.49−7.51 (m, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.66 (br s, 1H). MS (pos. APCI): 395.1 (M + 1).

Intramolecular Heck Endo-Cyclization of DHPM 4. A 2-mL microwave vial was charged with **4** (78.7 mg, 0.20 mmol), Herrman's palladacycle ($Pd_2(OAc)_2(P(o\text{-tol})_3)_2$, 9.4 mg, 0.010 mmol), DIPEA (0.105 mL, 0.60 mmol), 0.10 mL of H_2O and 0.90 mL of MeCN and then irradiated at 150 °C for 15 min. After cooling, the reaction mixture was filtered and evaporated to dryness. The residue was then purified by flash column chromatography (MeOH/$CHCl_3$) to produce 48.5 mg of **5** (78%).

5. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.11 (t, J = 7.1 Hz, 3H), 2.48 (s, 3H), 4.09 (q, J = 7.1 Hz, 2H), 5.74 (s, 1H), 6.45 (d, J = 12.2 Hz, 1H), 7.14−7.18 (m, 1H), 7.30 (d, J = 12.2 Hz, 1H), 7.38−7.47 (m, 3H), 8.58 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ 14.3, 18.5, 54.5, 60.7, 99.7, 124.5, 126.5, 128.9, 130.5, 131.1, 134.2, 138.1, 141.0, 148.0, 149.1, 165.1, 166.2. Anal. Calcd for $C_{17}H_{16}N_2O_4$ (%): C, 65.38; H, 5.16; N, 8.97. Found: C, 65.34; H, 5.19; N, 8.97.

Carbonylations of 4-(Bromophenyl)-DHPMs 1a−c Using $Mo(CO)_6$ as the Carbon Monoxide Source. A 2-mL microwave vial was charged with the appropriate DHPM **1** (50.9 mg, 0.15 mmol), Herrman's palladacycle ($Pd_2(OAc)_2(P(o\text{-tol})_3)_2$, 7.0 mg, 0.0075 mmol), Fu salt ($[(t\text{-Bu})_3PH]BF_4$) (8.7 mg, 0.030 mmol), $Mo(CO)_6$ (39.6 mg, 0.15 mmol), nucleophile (0.45 or 0.75 mmol or as solvent, amount specified in Table 1), DBU (0.067 mL, 0.45 mmol), and dry THF (1.0 mL). The vial was immediately capped with a Teflon septum and irradiated with microwaves for 15 min at the given temperature (Table 1). After cooling, the reaction mixture was filtered through a silica plug, and the solvent was removed under reduced pressure. Compounds **6a**−**f**, **6h**, and **6l**−**m** were purified by reversed-phase flash column chromatography using a MeCN in H_2O (0.05% HCOOH) manual gradient. Compounds **6i**,**j**, and **6n** were purified by flash column chromatography using MeOH in $CHCl_3$. Compounds **6g** and **6k** were purified by preparative RP-LC/MS using a MeCN in H_2O (0.05% HCOOH) gradient and UV-triggered fraction collection. Final evaporation of solvents gave the products **6a**−**n** in 21−87% yield (>95% pure by ^{1}H NMR).

6a. ^{1}H NMR (CD_3OD, 400 MHz): δ 0.97 (t, J = 7.4 Hz, 3H), 1.15 (t, J = 7.2 Hz, 3H), 1.40 (sext, J = 7.4 Hz, 2H), 1.55−1.64 (m, 2H), 2.35 (s, 3H), 3.36 (t, J = 7.2 Hz, 2H), 4.06 (q, J = 7.1 Hz, 3H), 5.37 (s, 1H), 7.40 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H). ^{13}C NMR (CD_3OD, 100.5 MHz): δ 14.1, 14.5, 18.2, 21.2, 32.6, 40.8, 56.0, 61.1, 101.6, 127.8, 128.6, 135.2, 149.2, 149.4, 154.9, 167.3, 169.8. Anal. Calcd for $C_{19}H_{25}N_3O_4$ (%): C, 63.49; H, 7.01; N, 11.69. Found: C, 63.30; H, 6.91; N, 11.44.

6b. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.11 (t, J = 7.1 Hz, 3H), 2.26 (s, 3H), 3.99 (q, J = 7.1 Hz, 2H), 5.23 (d, J = 3.6 Hz, 1H), 7.05−7.11 (m, 1H), 7.31−7.39 (m, 4H), 7.74−7.78 (m, 2H), 7.84 (br s, 1H), 7.90 (d, J = 8.4 Hz, 2H), 9.25 (s, 1H), 10.27 (s, 1H). ^{13}C NMR (DMSO-d_6, 100.5 MHz): δ 14.2, 18.0, 53.9, 59.5, 99.1, 120.5, 123.9, 126.4, 128.0, 128.8, 134.3, 139.2, 148.2, 148.9, 152.2, 165.4, 165.6. Anal. Calcd for $C_{21}H_{21}N_3O_4$ (%): C, 66.48; H, 5.58; N, 11.08. Found: C, 66.54; H, 5.69; N, 10.88.

6c. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.10 (t, J = 7.1 Hz, 3H), 2.26 (s, 3H), 3.98 (q, J = 7.1 Hz, 2H), 4.47 (d, J = 6.0 Hz, 2H), 5.20 (d, J = 3.4 Hz, 1H), 7.21−7.35 (m, 7H), 7.80 (br s, 1H), 7.84 (d, J = 8.3 Hz, 2H), 8.99 (t, J = 6.0 Hz, 1H), 9.25 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100.5 MHz): δ 14.1, 17.8, 42.6, 53.7, 59.3, 98.8, 126.2, 126.7, 127.1, 127.5, 128.3, 133.5, 139.7, 147.8, 148.7, 152.0, 165.2, 166.0. Anal. Calcd for $C_{22}H_{23}N_3O_4$ (%): C, 67.16; H, 5.89; N, 10.68. Found: C, 67.34; H, 5.75; N, 10.48.

6d. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.08 (t, J = 7.1 Hz, 3H), 2.26 (s, 3H), 3.93−4.01 (m, 2H), 4.48 (d, J = 6.1 Hz, 2H), 5.21 (d, J = 3.4 Hz, 1H), 7.20−7.45 (m, 7H), 7.76−7.82 (m, 3H), 9.05 (t, J = 6.1 Hz, 1H), 9.23 (br s, 1H). ^{13}C NMR (DMSO-d_6, 100.5 MHz): δ 14.0, 17.8, 42.6, 54.1, 59.2, 98.9, 125.8, 126.0, 126.7, 127.2, 128.3, 128.4, 129.1, 134.5, 139.7, 145.2, 148.6, 151.9, 165.2, 166.1. Anal. Calcd for $C_{22}H_{23}N_3O_4$ (%): C, 67.16; H, 5.89; N, 10.68. Found: C, 67.21; H, 5.83; N, 10.61.

6e. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.17 (t, J = 7.1 Hz, 3H), 2.33 (s, 3H), 3.30−3.90 (m, 4H), 4.08 (q, J = 7.1 Hz, 2H), 5.41 (d, J = 3.2 Hz, 1H), 6.16 (br s, 1H), 7.35 (s, 4H), 8.45 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ 14.3, 18.8, 55.3, 60.3, 67.0, 101.1, 126.9, 127.7, 135.0, 145.6, 146.9, 153.7, 165.6, 170.2. Anal. Calcd for $C_{19}H_{23}N_3O_5$ (%): C, 61.11; H, 6.21; N, 11.25. Found: C, 61.01; H, 6.17; N, 11.16.

6f. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.15 (t, J = 7.0 Hz, 3H), 2.33 (s, 3H), 3.28−3.88 (m, 4H), 4.00−4.11 (m, 2H), 5.40 (d, J = 3.2 Hz, 1H), 6.14 (br s, 1H), 7.27−7.39 (m, 4H), 8.37 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ 14.3, 18.8, 55.5, 60.2, 67.0, 100.9, 125.8, 126.7, 128.3, 129.1, 135.6, 144.4, 147.1, 153.4, 165.6, 170.2. Anal. Calcd for $C_{19}H_{23}N_3O_5$ (%): C, 61.11; H, 6.21; N, 11.25. Found: C, 60.89; H, 6.09; N, 11.32.

6g. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.17 (t, J = 7.1 Hz, 3H), 2.35 (s, 3H), 3.22−3.98 (m, 4H), 4.04−4.12 (m, 2H), 5.43 (d, J = 2.8 Hz, 1H), 5.77 (br s, 1H), 7.28−7.39 (m, 4H), 7.73 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ 14.4, 19.0, 55.7, 60.3, 67.0, 101.1, 125.8, 126.8, 128.3, 129.2, 135.7, 144.4, 146.7, 152.9, 165.6, 170.2. Anal. Calcd for $C_{19}H_{23}N_3O_5$ (%): C, 61.11; H, 6.21; N, 11.25. Found: C, 62.87; H, 6.92; N, 10.23.

6h. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.10 (t, J = 7.1 Hz, 3H), 2.27 (s, 3H), 4.00 (q, J = 7.1 Hz, 2H), 5.22 (s, 1H), 7.38 (d, J = 8.4 Hz, 2H), 7.49−7.63 (m, 3H), 7.85−7.95 (m, 4H), 10.47 (m, 2H). ^{13}C NMR (DMSO-d_6, 100.5 MHz): δ 14.1, 17.8, 53.8, 59.3, 98.7, 126.4, 127.4, 127.7, 128.5, 131.7, 131.9, 132.6, 148.5, 148.9, 152.0, 165.2, 165.6, 165.8. Anal. Calcd for $C_{22}H_{22}N_4O_5$ (%): C, 62.55; H, 5.25; N, 13.26. Found: C, 62.15; H, 5.43; N, 13.12.

6i. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.14 (t, J = 7.1 Hz, 3H), 2.32 (s, 3H), 3.89 (s, 3H), 4.01−4.09 (m, 2H), 5.43 (d, J = 2.9 Hz, 1H), 6.24 (br s, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.96 (d, J = 8.4 Hz, 2H), 8.57 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ 14.3, 18.8, 52.3, 55.5, 60.3, 100.9, 126.9, 127.8, 129.9, 130.2, 147.1, 148.6, 153.7, 165.6, 166.8. Anal. Calcd for $C_{16}H_{18}N_2O_5$ (%): C, 60.37; H, 5.70; N, 8.80. Found: C, 60.10; H, 5.56; N, 8.68.

6j. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.08 (t, J = 7.1 Hz, 3H), 2.28 (s, 3H), 3.83 (s, 3H), 3.93−4.02 (m, 2H), 5.34 (s,

1H), 6.76 (br s, 1H), 7.32 (t, $J = 7.7$ Hz, 1H), 7.45 (d, $J = 7.7$, Hz, 1H), 7.85 (d, $J = 7.7$ Hz, 1H), 7.89 (s, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ 14.0, 18.3, 52.2, 55.2, 60.2, 100.6, 128.0, 128.9, 129.1, 130.3, 131.4, 144.4, 147.3, 153.3, 165.8, 167.1. Anal. Calcd for $C_{16}H_{18}N_2O_5$ (%): C, 60.37; H, 5.70; N, 8.80. Found: C, 60.49; H, 5.81; N, 8.94.

6k. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.98 (t, $J = 7.1$ Hz, 3H), 2.45 (s, 3H), 3.92−4.00 (m, 5H), 5.95 (d, $J = 3.2$ Hz, 1H), 6.37 (br s, 1H), 7.30−7.36 (m, 2H), 7.48 (ddd, $J = 7.6$, 7.6, 1.6 Hz, 1H), 7.91 (dd, $J = 7.6$, 1.6 Hz, 1H), 8.46 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ 14.1, 18.6, 52.0, 52.6, 60.0, 99.4, 127.5, 127.9, 128.7, 131.0, 133.2, 143.6, 148.8, 153.0, 165.7, 168.3. Anal. Calcd for $C_{16}H_{18}N_2O_5$ (%): C, 60.37; H, 5.70; N, 8.80. Found: C, 60.15; H, 5.56; N, 8.69.

6l. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.15 (t, $J = 7.1$ Hz, 3H), 2.33 (s, 3H), 4.05 (q, $J = 7.1$ Hz, 2H), 5.34 (s, 2H), 5.43 (d, $J = 3.2$ Hz, 1H), 6.11 (br s, 1H), 7.30−7.45 (m, 7H), 8.01 (d, $J = 8.4$ Hz, 2H), 8.38 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ 14.3, 18.8, 55.5, 60.3, 66.8, 100.9, 126.8, 128.3, 128.4, 128.7, 129.8, 130.4, 136.1, 147.1, 153.5, 165.5, 166.1. Anal. Calcd for $C_{22}H_{22}N_2O_5$ (%): C, 66.99; H, 5.62; N, 7.10. Found: C, 67.13; H, 5.74; N, 7.17.

6m. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.19 (t, $J = 7.1$ Hz, 3H), 2.38 (s, 3H), 4.10 (q, $J = 7.1$ Hz, 2H), 5.51 (d, $J = 3.1$ Hz, 1H), 5.85 (br s, 1H), 7.18−7.22 (m, 2H), 7.25−7.30 (m, 1H), 7.38−7.45 (m, 2H), 7.48 (d, $J = 8.4$ Hz, 2H), 7.88 (br s, 1H), 8.16 (d, $J = 8.4$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ 14.4, 19.1, 55.7, 60.4, 101.1, 121.8, 126.1, 127.0, 129.4, 129.7, 130.9, 146.8, 149.2, 151.0, 152.9, 164.9, 165.5. Anal. Calcd for $C_{21}H_{22}N_2O_5 + 0.1H_2O$ (%): C, 65.99; H, 5.33; N, 7.33. Found: C, 65.83; H, 5.47; N, 7.26.

6n. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.08 (s, 9H), 1.09−1.17 (m, 5H), 2.35 (s, 3H), 4.03−4.11 (m, 2H), 4.38−4.43 (m, 2H), 5.45 (d, $J = 2.9$ Hz, 1H), 5.88 (br s, 1H), 7.38 (d, $J = 8.4$ Hz, 2H), 7.98 (d, $J = 8.4$ Hz, 2H), 8.23 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ −1.3, 14.3, 17.5, 18.9, 55.7, 60.3, 63.5, 101.0, 126.8, 130.2, 130.5, 146.9, 148.4, 153.4, 165.4, 166.5. Anal. Calcd for $C_{20}H_{28}N_2O_5Si$ (%): C, 59.38; H, 6.98; N, 6.92. Found: C, 59.54; H, 7.10; N, 6.95.

Using 4-(Bromophenyl)-DHPMs 1a,b as Arylating Agents for Palladium-Catalyzed N-Arylations of Amides and Carbamates. A 2-mL microwave vial was charged with DHPM **1a** or **1b** (50.9 mg, 0.15 mmol), $RCONH_2$ (0.30 mmol of amide or 0.75 mmol, 87.9 mg of *tert*-butylcarbamate), $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol), Xantphos (6.5 mg, 0.011 mmol), and Cs_2CO_3 (98 mg, 0.30 mmol). Dry THF was added, and the mixture was irradiated at the temperature specified in Table 2 for 15 min. Flash column chromatography (MeOH/$CHCl_3$) produced the pure N-arylated compounds **7a**−**e** in 62−88% yield.

7a. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.09 (t, $J = 7.1$ Hz, 3H), 2.02 (s, 3H), 2.24 (s, 3H), 3.98 (q, $J = 7.1$ Hz, 2H), 5.09 (d, $J = 3.3$ Hz, 1H), 7.14 (d, $J = 8.6$ Hz, 2H), 7.49 (d, $J = 8.6$ Hz, 2H), 7.67 (br s, 1H), 9.15 (br s, 1H), 9.91 (br s, 1H). ^{13}C NMR (DMSO-d_6, 100.5 MHz): δ 14.1, 17.7, 23.9, 53.6, 59.2, 99.3, 119.0, 126.6, 138.4, 139.5, 148.1, 152.1, 165.4, 168.2. Anal. Calcd for $C_{16}H_{19}N_3O_4$ (%): C, 60.56; H, 6.03; N, 13.24. Found: C, 60.71; H, 5.92; N, 13.06.

7b. ^{1}H NMR (CD_3OD, 400 MHz): δ 1.15 (t, $J = 7.1$ Hz, 3H), 2.10 (s, 3H), 2.34 (s, 3H), 4.06 (q, $J = 7.1$ Hz, 2H), 5.30 (s, 1H), 7.05 (dt, $J = 7.9$, 1.5 Hz, 1H), 7.25 (t, $J = 7.9$ Hz, 1H), 7.45 (m, 1H), 7.54 (t, $J = 2.0$ Hz, 1H). ^{13}C NMR (CD_3OD, 100.5 MHz): δ 14.5, 18.1, 23.8, 56.4, 61.1, 101.9, 119.4, 120.4, 123.4, 130.0, 140.2, 146.5, 149.0, 154.9, 167.5, 171.7. Anal. Calcd for $C_{16}H_{19}N_3O_4$ (%): C, 60.56; H, 6.03; N, 13.24. Found: C, 60.48; H, 6.15; N, 13.08.

7c. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.12 (t, $J = 7.1$ Hz, 3H), 2.27 (s, 3H), 4.00 (q, $J = 7.1$ Hz, 2H), 5.14 (d, $J = 3.3$ Hz, 1H), 7.22 (d, $J = 8.6$ Hz, 2H), 7.49−7.61 (m, 3H), 7.69−7.74 (m, 3H), 7.93−7.97 (m, 2H), 9.18 (d, $J = 2.1$ Hz, 1H), 10.2 (br s, 1H). ^{13}C NMR (DMSO-d_6, 100.5 MHz): δ 14.1, 17.8, 53.6, 59.2, 99.3, 120.4, 126.5, 127.6, 128.4, 131.6, 134.9, 138.2, 140.2, 148.2, 152.1, 165.4, 165.5. Anal. Calcd for $C_{21}H_{21}N_3O_4$ (%): C, 66.48; H, 5.58; N, 11.08. Found: C, 66.56; H, 5.71; N, 11.18.

7d. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.12 (t, $J = 7.1$ Hz, 3H), 2.26 (s, 3H), 4.00 (q, $J = 7.1$ Hz, 2H), 5.15 (d, $J = 3.6$ Hz, 1H), 7.00 (d, $J = 7.6$ Hz, 1H), 7.29 (t, $J = 7.8$ Hz, 1H), 7.50−7.61 (m, 3H), 7.66−7.76 (m, 3H), 7.92−7.96 (m, 2H), 9.18 (d, $J = 2.0$ Hz, 1H), 10.28 (br s, 1H). ^{13}C NMR (DMSO-d_6, 100.5 MHz): δ 14.1, 17.9, 54.7, 59.2, 99.1, 118.4, 119.4, 121.9, 127.7, 128.4, 128.5, 131.5, 135.0, 139.3, 145.5, 148.3, 151.9, 165.4, 165.6. Anal. Calcd for $C_{21}H_{21}N_3O_4$ (%): C, 66.48; H, 5.58; N, 11.08. Found: C, 66.74; H, 5.71; N, 10.95.

7e. ^{1}H NMR (CD_3OD, 400 MHz): δ 1.16 (t, $J = 7.1$ Hz, 3H), 1.50 (s, 9H), 2.33 (s, 3H), 4.01−4.09 (m, 2H), 5.26 (s, 1H), 7.20 (d, $J = 8.8$ Hz, 2H), 7.34 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR (CD_3OD, 100.5 MHz): δ 14.5, 18.1, 28.7, 55.9, 61.0, 80.9, 102.2, 119.8, 128.1, 140.0, 140.1, 148.6, 155.0, 155.3, 167.5. Anal. Calcd for $C_{19}H_{25}N_3O_5$ (%): C, 60.79; H, 6.71; N, 11.19. Found: C, 60.90; H, 6.74; N, 11.17.

Copper-Catalyzed Goldberg N3-Arylation of DHPMs. A mixture of DHPM **8a** or **8b** (0.5 mmol), the corresponding aryl iodide (0.75 mmol), CuI (0.1 mmol, 20 mg), and Cs_2CO_3 (0.75 mmol, 244 mg) in anhydrous DMF (200 μL) was irradiated in a 2-mL microwave vial at 180 °C for 40 min. After cooling, the reaction mixture was filtered through a plug of 0.5 cm of silica (cartridge i.d.: 60 × 12 mm) eluting with 5 mL of DCM/EtOAc 1:1. The filtrate was evaporated and the residue was purified by automated flash chromatography (DCM/EtOAc) to give DHPMs **9a**−**j** as pale yellow oils in 13−83% isolated yield.

9a. ^{1}H NMR ($CDCl_3$, 360 MHz): δ 1.28 (t, $J = 7.1$ Hz, 3H), 2.54 (s, 3H), 3.28 (s, 3H), 3.71 (s, 3H), 4.15−4.27 (m, 2H), 5.73 (s, 1H), 6.71−6.78 (m, 3H), 7.20 (t, $J = 8.1$ Hz, 1H), 7.25−7.32 (m, 5H). MS (pos. APCI): 381.3 (M + 1).

9b. ^{1}H NMR ($CDCl_3$, 360 MHz): δ 1.28 (t, $J = 7.1$ Hz, 3H), 2.32 (s, 3H), 2.54 (s, 3H), 3.29 (s, 3H), 4.15−4.26 (m, 2H), 5.70 (s, 1H), 7.02 (d, $J = 8.4$ Hz, 2H), 7.10 (d, $J = 8.3$ Hz, 2H), 7.24−7.32 (m, 5H), MS (pos. APCI): 365.1 (M + 1).

9c. ^{1}H NMR ($CDCl_3$, 360 MHz): δ 1.29 (t, $J = 7.1$ Hz, 3H), 2.55 (s, 3H), 3.29 (s, 3H), 4.16−4.28 (m, 2H), 5.76 (s, 1H), 7.15−7.33 (m, 10H). MS (pos. APCI): 351.3 (M + 1).

9d. ^{1}H NMR ($CDCl_3$, 360 MHz): δ 1.23 (t, $J = 7.1$ Hz, 3H), 2.37 (s, 3H), 4.09−4.20 (m, 2H), 5.66 (s, 1H), 7.09−

7.12 (m, 2H), 7.23−7.32 (m, 8H), 7.69 (br s, 1H). ^{13}C NMR (DMSO-d_6, 90 MHz): δ 165.4, 151.6, 148.0, 142.7, 141.4, 129.2, 129.0, 128.2, 127.1, 126.8, 101.6, 63.2, 60.0, 18.07, 14.5; MS (pos. APCI): 337.2 (M + 1).

9e. ^{1}H NMR ($CDCl_3$, 360 MHz): δ 1.29 (t, J = 7.1 Hz, 3H), 2.54 (s, 3H), 3.29 (s, 3H), 4.17−4.27 (m, 2H), 5.70 (s, 1H), 7.09 (d, J = 8.6 Hz, 2H), 7.23−7.31 (m, 7H), MS (pos. APCI): 385.2 (M + 1).

9f. ^{1}H NMR ($CDCl_3$, 360 MHz): δ 1.21 (t, J = 7.1 Hz, 3H), 2.61 (s, 3H), 3.32 (s, 3H), 3.82 (s, 3H), 4.10−4.20 (m, 2H), 5.61 (s, 1H), 7.24−7.35 (m, 8H), 7.97 (d, J = 7.3 Hz, 1H). MS (pos. APCI): 409.2 (M + 1).

9g. ^{1}H NMR ($CDCl_3$, 360 MHz): δ 1.31 (t, J = 7.1 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H), 2.53 (s, 3H), 3.27 (s, 3H), 4.20−4.31 (m, 2H), 4.36 (q, J = 7.1 Hz, 2H), 5.85 (s, 1H), 7.24−7.32 (m, 7H), 7.98 (d, J = 8.8 Hz, 2H). MS (pos. APCI): 423.3 (M + 1).

9h. ^{1}H NMR ($CDCl_3$, 360 MHz): δ 1.25 (t, J = 7.1 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H), 2.38 (s, 3H), 4.12−4.23 (m, 2H), 4.36 (q, J = 7.2 Hz, 2H), 5.76 (s, 1H), 7.23−7.29 (m, 7H), 7.73 (br s, 1H), 7.98 (d, J = 8.6 Hz, 2H). MS (pos. APCI): 409.2 (M + 1).

9i. ^{1}H NMR ($CDCl_3$, 360 MHz): δ 1.32 (t, J = 7.1 Hz, 3H), 2.53 (s, 3H), 2.57 (s, 3H), 3.27 (s, 3H), 4.20−4.32 (m, 2H), 5.88 (s, 1H), 7.25−7.33 (m, 7H), 7.91 (d, J = 8.8 Hz, 2H). MS (pos. APCI): 393.3 (M + 1).

9j. ^{1}H NMR ($CDCl_3$, 360 MHz): δ 1.34 (t, J = 7.1 Hz, 3H), 2.53 (s, 3H), 3.27 (s, 3H), 4.23−4.35 (m, 2H), 5.92 (s, 1H), 7.25−7.41 (m, 7H), 8.16−8.19 (m, 2H). MS (pos. APCI): 396.3 (M + 1).

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