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Ru(II)-Catalyzed C−H Activation: Amide-Directed 1,4-Addition of the Ortho C−H Bond to Maleimides

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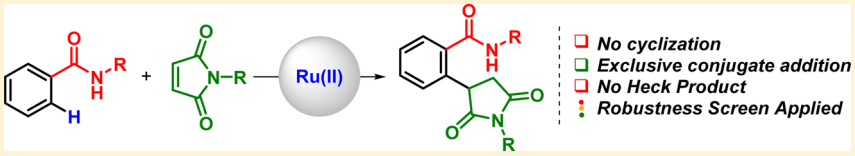
Supporting Information



ABSTRACT: Maleimide has been used as a selective coupling partner to generate conjugate addition products exclusively. The typical Heck-type oxidative coupling that occurs when alkenes are used is avoided by choosing maleimide as an alkene, which cannot undergo β-hydride elimination due to the unavailability of a *syn*-periplanar β-hydrogen atom. The amide nitrogen, which is notorious for undergoing tandem reactions to generate spirocyclic or annulation products under cross-coupling conditions, remains innocent in this report. Along with the substrate scope, a robustness screen has been performed to analyze the performance of amide as a directing group in the presence of other directing groups and also to examine the tolerance of the reaction conditions for other frequently encountered functional groups.

INTRODUCTION

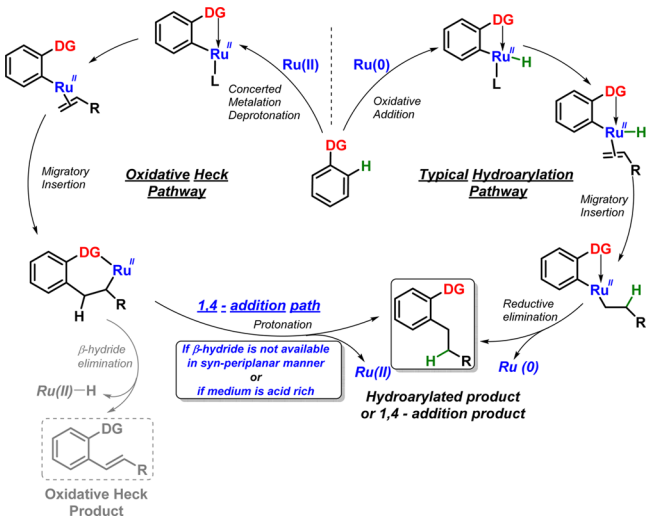
Functionalization of arenes at the *ortho*-position by employing a directing group strategy is well-known.[1] Various metal catalysts have been used to achieve such functionalization of arenes; however, the Pd catalysts have, by and large, dominated this arena.[2] Ruthenium, a much cheaper metal than palladium,[3] has been under-represented in this area.[4] Nonetheless, the pioneering work by Murai[5] and others[6] has resulted in an increased number of reports of *ortho*-functionalization of arenes using Ru catalysts. In continuation of our work in this area,[7] we initiated studies toward the use of diverse coupling partners with traditional directing groups.

The hydroarylation reaction is a useful method to add an arene across an alkene or alkyne.[8] Ru(0) catalysts/precursors have been traditionally[5,8] used for hydroarylation across an alkene, wherein the metal inserts into the C−H bond at the *ortho*-position. This oxidative addition process generates a reactive C(sp^2)−Ru−H species[9] that undergoes an insertion reaction with an alkene. Further, the metal is ejected via a reductive elimination process to create a new bond between the arene and the coupling partner (Scheme 1). Here, the metal goes through a cycle of redox reactions, typically from Ru(0) to Ru(II) and back to Ru(0). Ru(0) catalysts are often not stable to air and water, a property that limits the wide application of a method.[10] There have been some reports on generating Ru(0) catalysts in situ using the more stable and easy to handle Ru(II) or Ru(III) catalysts.[10,11]

An alternate pathway to obtain hydroarylated products using Ru(II) catalysts is to choose a substrate that undergoes protonation faster than β-hydride elimination. This can be achieved by ensuring that the β-hydrogen for β-hydride elimination is not available in a *syn*-periplanar fashion and keeping the reaction medium rich in acid (Scheme 1). In view of this difference in the mechanism, it would be more fitting to call this second pathway a 1,4-addition or conjugate addition. We have recently demonstrated the use of maleimide as an effective coupling partner to yield conjugate addition products (Scheme 2) under Ru(II) catalysis.[12]

Amide as a directing group has been fairly well explored,[13] and several reactions yield products in which amide (especially the nitrogen atom) also undergoes transformations to eventually yield products that are bicyclic or spirocyclic (Scheme 2).[14] Hence, amides are non-innocent directing groups, and to preserve them without undergoing any further transformations

Scheme 1. Mechanistic Hypothesis for the Work



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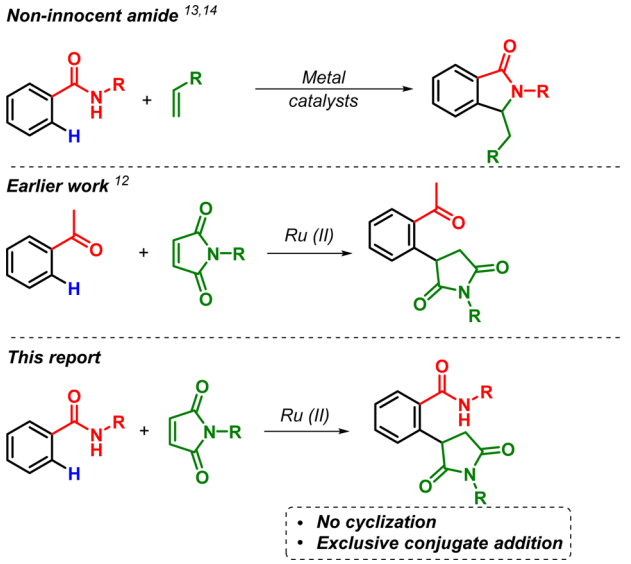
Scheme 2. Comparison of Previous Reports and Current Report



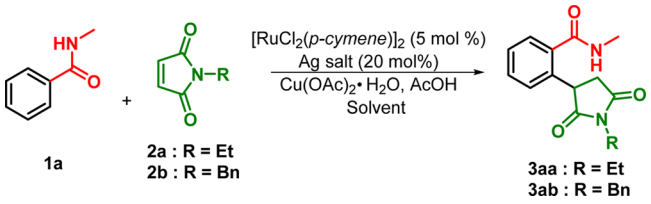
in the reaction medium is a challenge. Reports in this direction are scanty.[15]

RESULTS AND DISCUSSION

Optimization of Reaction Conditions. We started our investigation with *N*-methylbenzamide (**1a**) and *N*-benzylmaleimide (**2b**) as benchmark substrates. Our initial studies started with 5 mol % of $[RuCl_2(p\text{-cymene})]_2$ as the catalyst, 20 mol % of $AgSbF_6$ as the activator, 1 equiv of $Cu(OAc)_2.H_2O$ as a source of acetate ions, and 10 equiv of AcOH as protonating source, which furnished 70% of the requisite product (**3ab**, entry 1, Table 1). Without AcOH, the yield decreased to 41% (entry 2), which clearly revealed the importance of acetic acid in the reaction. However, using a large excess of AcOH (30 equiv) did not improve the yield (entry 3). Increasing the amount of maleimide **2b** (2 equiv) did not enhance the yield of **3ab** (entry 4) and neither did decreasing the amount of **2b** to 1.1 equiv (entry 5, 63% yield). By replacing *N*-benzylmaleimide (**2b**) with *N*-ethylmaleimide (**2a**), we observed a dramatic increase in yield (entry 6, 85%). Performing the reaction at either higher temperature (120 °C, entry 7, 57%) or lower temperature (80 °C, entry 8, 74%) did not bring any improvement to the outcome of the reaction. When the reaction was performed in argon atmosphere it gave the same yield of **3aa** as before (85%, entry 9). Decreasing the catalyst amount to 2.5 mol % of Ru, and 10 mol % of Ag provided only 74% yield of the product (entry 10). Varying the amount of Cu catalyst also did not help (entries 11 and 12). Changing the solvent to acetonitrile or DMF was found to be detrimental to the yield of the product (entries 13 and 14). Eventually, the silver activator was changed to $AgNTf_2$, and it provided a marginal increase in the yield of the expected product **3aa** (87%, entry 15). To our surprise, changing the activator to $AgBF_4$ proved to be very helpful, and the yield increased to 95% (entry 16). Hence, Ru (5 mol %), $AgBF_4$ (20 mol %), $Cu(OAc)_2{\cdot}H_2O$ (1.5 equiv), and acetic acid (10 equiv) in dichloroethane solvent at 100 °C were established as the best conditions to carry out the reaction.

Substrate Scope. With an optimized catalytic system in hand, we explored the scope of the reaction (Scheme 3). For all of the substrate scope reactions, neither the starting material

Table 1. Optimization Table[a]



entry	malemide (equiv)	activator	AcOH (equiv)	temp (°C)	solvent	yield[b] (%)
1	R = Bn (1.5)	$AgSbF_6$	10	100	DCE	70
2	R = Bn (1.5)	$AgSbF_6$	0	100	DCE	41
3	R = Bn (1.5)	$AgSbF_6$	30	100	DCE	44
4	R = Bn (2.0)	$AgSbF_6$	10	100	DCE	65
5	R = Bn (1.1)	$AgSbF_6$	10	100	DCE	63
6	R = Et (1.5)	$AgSbF_6$	10	100	DCE	85
7	R = Et (1.5)	$AgSbF_6$	10	120	DCE	57
8	R = Et (1.5)	$AgSbF_6$	10	80	DCE	74
9	R = Et (1.5)	$AgSbF_6$	10	100	DCE	85[c]
10	R = Et (1.5)	$AgSbF_6$	10	100	DCE	74[d]
11	R = Et (1.5)	$AgSbF_6$	10	100	DCE	68[e]
12	R = Et (1.5)	$AgSbF_6$	10	100	DCE	75[f]
13	R = Et (1.5)	$AgSbF_6$	10	100	CH_3CN	42
14	R = Et (1.5)	$AgSbF_6$	10	100	DMF	NR
15	R = Et (1.5)	$AgNTf_2$	10	100	DCE	87
16	**R = Et (1.5)**	**$AgBF_4$**	**10**	**100**	**DCE**	**95 (91)**

[a]Reaction conditions: **1a** (0.3 mmol), **2a/b** (1.5 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), Ag salt (20 mol %), $Cu(OAc)_2{\cdot}H_2O$ (1.5 equiv), AcOH (10 equiv), DCE (2.0 mL), 100 °C. [b]NMR yield of the product using terephthaldehyde as the internal standard; isolated yield in parentheses. [c]Reaction was performed in Ar atmosphere. [d]2.5 mol % of Ru and 10 mol % of Ag was used. [e]Reaction was performed with 2.0 equiv of Cu catalyst. [f]Reaction was performed with 1.0 equiv of Cu catalyst.

nor the maleimide partner was ever detected in significant amounts postreaction, indicating that these components of the reaction underwent decomposition. For this reason, the thin-layer chromatograms would generally be messy. Compounded with this problem was the high polarity of the final product due to the amide and succinimide groups in the same molecule. Due to this increased polarity of the product and decomposition of starting materials, purification was not easy, and isolated products were frequently found to be contaminated with uncharacterized impurities. Washing the reaction mixture or the final isolated products with either acid or base or column purification with different mesh sizes of silica or alumina were not found to greatly enhance the product purity. Wherever extensive decomposition was observed, lower yields of the product have been reported.

The electron-rich benzamide derivatives such as 4-methoxy-*N*-methylbenzamide (**1b**) with (**2a**) under the optimal reaction conditions gave 86% of the expected hydroarylated product **3ba** when $AgSbF_6$ was used instead of $AgBF_4$ (Scheme 3). The 3-methoxy-*N*-methylbenzamide derivative furnished a low yield of the corresponding product (**3ca**, 40%). However, ortho-substituted derivatives like 2-chloro-*N*-methylbenzamide (**1d**), 2-iodo-*N*-methylbenzamide (**1e**), 2-methyl-*N*-methylbenzamide (**1f**), and *N*-methyl-[1,1′-biphenyl]-2-carboxamide (**1g**) furnished excellent yields of the corresponding products **3da**, **3ea**, **3fa**, and **3ga**, respectively (91, 68, 51, and 79%, respectively). To our surprise, the bulky substitution on the *ortho*-position of the benzamide derivative did not hamper the reaction, and the reaction of a *o*-styryl-substituted benzamide

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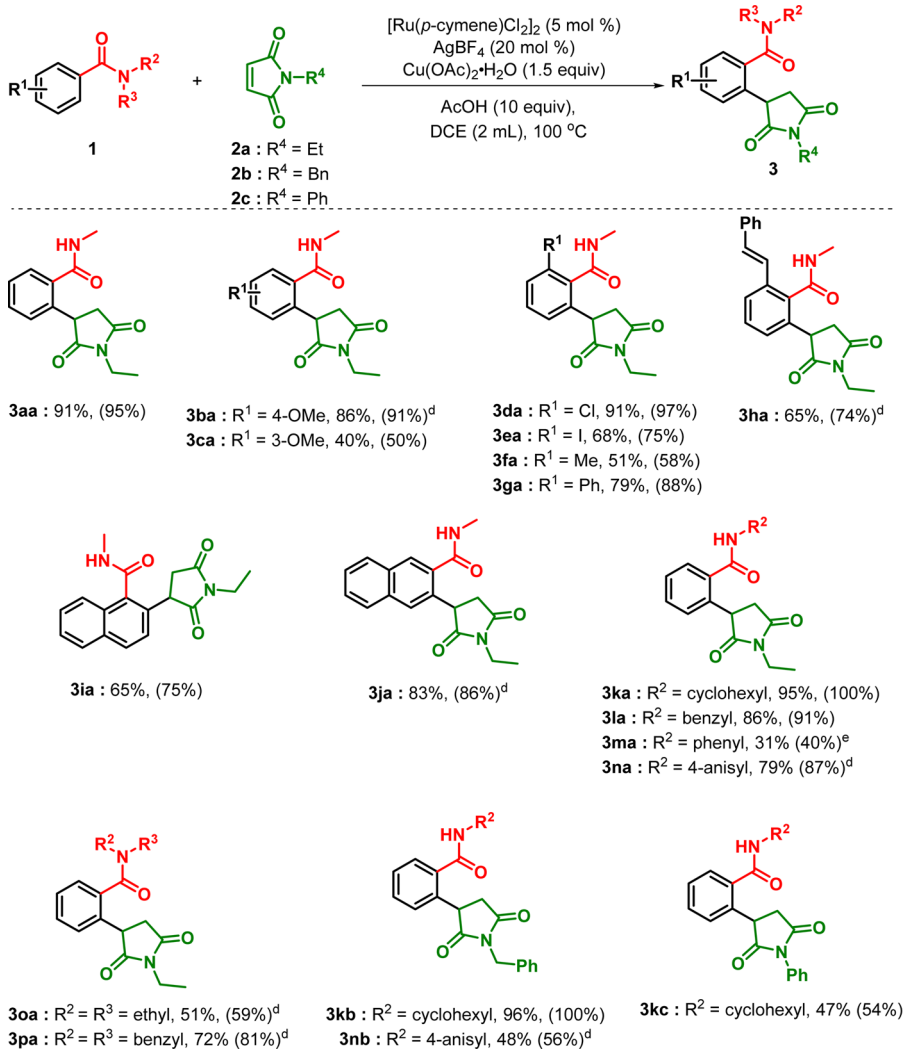
Scheme 3. Substrate Scope for Benzamide[a–c]



[a]Standard reaction conditions: 1 (0.3 mmol), **2** (1.5 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $AgBF_4$ (20 mol %), $Cu(OAc)_2.H_2O$ (1.5 equiv), AcOH (10 equiv), DCE (2.0 mL), 100 °C. [b]Isolated yields. [c]NMR yields in parentheses, obtained by using terephthaldehyde as internal standard. [d]Reaction was performed with $AgSbF_6$, instead of $AgBF_4$. [e]Unreacted starting material = 55%.

derivative (**1h**) with **2a** furnished the expected hydroarylated product **3ha** in 65% yield. Naphthalene derivatives such as *N*-methyl-1-naphthamide (**1i**) and *N*-methyl-2-naphthamide (**1j**) underwent a smooth reaction with *N*-ethylmaleimide (**2a**) under optimal reaction conditions and produced the corresponding products **3ia** and **3ja**, respectively, in good to excellent yields (65 and 83%, respectively). On the other hand, in the reactions of substrates with different substituents on the nitrogen atom of amide, such as *N*-cyclohexylbenzamide (**1k**) and *N*-benzylbenzamide (**1l**), with *N*-ethylmaleimide (**2a**), the corresponding hydroarylated products **3ka** and **3la** were obtained excellent yields (95 and 86%, respectively). However, *N*-phenylbenzamide (**1m**) under similar reaction with *N*-ethylmaleimide (**2a**) gave only 31% of the expected product (**3ma**) where around 40% of the starting material was left even after 24 h. Surprisingly, 4-methoxy-*N*-(4-methoxyphenyl)-benzamide (**1n**) reacted smoothly with **2a** to provide 79% yield of **3na**. The reactions of disubstituted amides such as *N*,*N*-diethylbenzamide (**1o**) and *N*,*N*-dibenzylbenzamide (**1p**) furnished the corresponding hydroarylated products **3oa** and **3pa** in moderate to good yields (51 and 72%, respectively). Next, we changed the maleimide derivative to *N*-benzylmaleimide and found that the reaction of the cyclohexyl derivative of benzamide (**1k**) as a coupling partner furnished 96% yield of **3kb**, whereas the 4-OMe derivative (**1n**) furnished only a moderate yield of **3nb** (48%). On reacting *N*-phenylmaleimide (**2c**) with *N*-cyclohexylbenzamide (**1k**), the expected product **3kc** was obtained in 47% yield.

Acetanilide as Substrate. After studying the benzamides as the directing group, we thought it was relevant to study the reaction of acetanilide with maleimides. Under the optimized reaction conditions that were employed for the reaction of benzamide with maleimides (entry 16, Table 1), the reaction of acetanilide with maleimides furnished poor yields of the corresponding hydroarylated products (**6**). Therefore, several conditions were examined to carry out this transformation effectively, and we were unable to optimize the reaction to obtain good yields. In these attempts, it was found that acetanilide was decomposing rapidly under the reaction conditions. When the temperature was reduced to 80 °C, and the reaction

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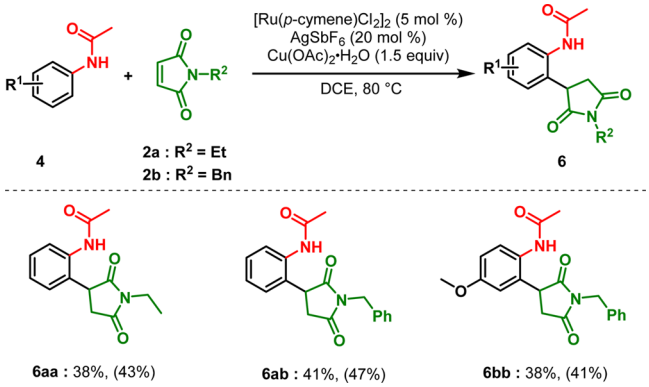
was carried out in the absence of AcOH, we were able to obtain the hydroarylated products in moderate yields. Thus, the reaction of acetanilide with *N*-ethylmaleimide afforded the hydroarylated product **6aa** in 38% isolated yield (Scheme 4). On changing to

Scheme 4. Substrate Scope for Acetanilide[a−c]



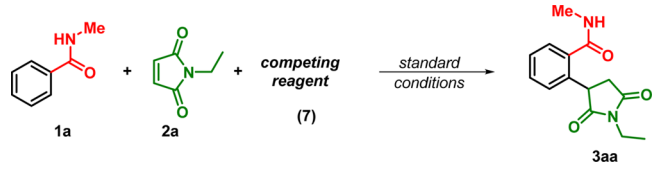
[a]Reaction conditions: **4** (0.3 mmol), **2** (1.5 equiv), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %), $AgSbF_6$ (20 mol %), $Cu(OAc)_2.H_2O$ (1.5 equiv), DCE (2.0 mL), 80 °C. [b]Isolated yields [c]NMR yields in parentheses, obtained by using terephthaldehyde as internal standard.

N-benzylmaleimde, we obtained 41% of the expected product (**6ab**), and by using *N*-(4-methoxyphenyl)acetamide (**4b**), we obtained only 38% of the corresponding product (**6bb**).

Robustness Screening. After exploring the substrate scope of the reaction, we thought it would be appropriate to explore this reaction in the presence of other directing groups. Since constructing molecules which have multiple similar functional groups requires multiple steps and can be cumbersome, we employed the strategy described by Glorius et al.[16] for exploring the tolerance of the reaction in the presence of other directing groups as well as functional groups. Accordingly, we setup a robustness screen to evaluate two aspects of the reaction: (i) to identify a potential "strong directing group", i.e., to check if the metal component of the reaction can effectively bind to a different directing group and, hence, deter the formation of the expected product **3aa** and (ii) to check if other directing groups "survive" the standard reaction conditions. The robustness screen acts as an indirect method to evaluate functional group tolerance and is operationally simple. However, it cannot evaluate the effects of electronic factors which a functional group imposes on the directing abilities of the amide group. Along with a robustness screen for directing group tolerance (Table 2), we also decided to include several random molecules (Table 3). The standard reaction with **1a** and **2a** as the coupling partners in the standard reaction conditions furnishes **3aa** in 95% yield (entry 16, Table 1). This reaction was then repeated in the presence of a variety of additives (1 equiv), and the yield of product **3aa** as well as the amount of additive (**7** or **8**) and starting materials (**1a** and **2a**) remaining after the reaction were determined. In all cases, the amount of **2a** left was less than 10%, indicating that maleimide decomposes extensively, and hence, 1.5 equiv is required for the reaction (Tables 2 and 3).

Effect of Other Directing Groups. Different directing groups like ketone, aldehyde, carboxylic acid, ester, amide, 2-phenylpyridine, and oxime were used in the form of simple compounds (**7a−g**). In the case of oxygen-based directing groups such as ketone, aldehyde, carboxylic acid, and *N*-benzoylindole (**7a−e**), the yield of **3aa** was comparable to

Table 2. Robustness Screening: Various Directing Groups[a−c]



entry	competing reagent (**7**, 1 equiv)	Yield (**3aa**,%)	**7** left (%)	**1a** left (%)	entry	competing reagent (**7**, 1 equiv)	Yield (**3aa**,%)	**7** left (%)	**1a** left (%)
1	(7a)	95 ●	15 ●	0	5	(7g)	95 ●	95 ●	0
2	(7b)	90 ●	4 ●	0	6	(7f)	0 ●	0 ●	100
3	(7c)	90 ●	90 ●	0					
4	(7d)	87 ●	7 ●	0	7	(7e)	0 ●	60 ●	100

● < 35% ● 35 - 65% ● > 65%

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (1.5 equiv), **7** or **8** (1 equiv), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %), $AgBF_4$ (20 mol %), $Cu(OAc)_2.H_2O$ (1.5 equiv), AcOH (10 equiv), DCE (2.0 mL), 100 °C. [b]Yield values were obtained by using terephthaldehyde as an internal standard for ^{1}H NMR. [c]In all cases, the amount of maleimide (**2a**) was less than 10%.

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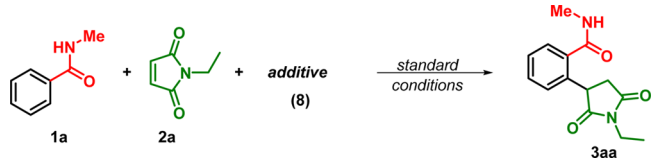
Table 3. Robustness Screening: Functional Group Tolerance[a–c]



3aa

Entry	Competing reagent (8, 1 equiv)	Yield (3aa,%)	8 left (%)	1a left (%)	Entry	Competing reagent (8, 1 equiv)	Yield (3aa,%)	8 left (%)	1a left (%)
1	(8a)	95 ●	-	0	7	(8g)	38 ●	-	56
2	(8b)	0 ●	-	100	8	(8h)	91 ●	23 ●	0
3	(8c)	4 ●	90 ●	83	9	(8i)	5 ●	9 ●	78
4	(8d)	90 ●	-	0	10	(8j)	0 ●	35 ●	100
5	(8e)	41 ●	70 ●	57	11	(8k)	2 ●	-	95
6	(8f)	93 ●	37 ●	0					

● < 35% ● 35 - 65% ● > 65%

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (1.5 equiv), **7** or **8** (1 equiv), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %), $AgBF_4$ (20 mol %), $Cu(OAc)_2.H_2O$ (1.5 equiv), AcOH (10 equiv), DCE (2.0 mL), 100 °C. [b]Yield values were obtained by using terephthaldehyde as an internal standard in ^1H NMR. [c]In all cases, the amount of maleimide (**2a**) was less than 10%.

that obtained under additive-free conditions (Table 2). However, we observed extensive decomposition of acetophenone, aldehyde, and ester (entries 1, 2, and 4, respectively, Table 2), whereas acid and *N*-benzoylindole (entries 3 and 5) were found to be more or less intact.

In none of the cases were conjugate addition products with the additives observed. It is interesting to note that the conjugate additions with ketone and *N*-benzoyl indole were reported by our own laboratory.[12] This indicates that aromatic amides are more reactive than aromatic ketones and indole amides as a directing group. In the case of nitrogen-based directing groups (entries 6 and 7), the formation of the required product **3aa** was not observed, which can be attributed to an irreversible complexation of these molecules with the metal catalyst, but the starting material (**1a**) was intact.

Effect of Other Functionalities. When different functionalities were chosen to be evaluated in a robustness screen for functional groups (**8a–k**), we obtained mixed results, and no rationale could be pin-pointed for the decrease in yield of **3aa** (Table 3). Molecules bearing one or more of the functional groups such as double bond, triple bond, alcohol, enol, nitrile, and halides (entries 1–8) were evaluated in this robustness screen, along with some heterocycles like benzoxazole, indole, and pyridine (entries 9–11). In very few cases, such as styrene, butanol, coumarin, and iodobenzene, the yield of **3aa** was intact (entries 1, 4, 6, and 8, respectively), but the additives had undergone significant decomposition. In the case of phenol and nitrile (entries 5 and 7, respectively), the yield of **3aa** was significantly reduced, while in the case of phenylacetylene, diphenylacetylene, benzoxazole, indole, and bromopyridine (entries 2, 3, 9, 10, and 11, respectively) the product was observed in very low yields. Based on the robustness study, we can see that amide is a powerful and strong directing group, and the reaction is fairly tolerant toward the presence of other functional groups. Even in the presence of other directing groups, we have observed only the products formed from the control amide. However, the presence of heterocycles was found to be detrimental to the formation of the product.

CONCLUSION

In this paper, we have presented a novel Ru(II)-catalyzed C–H functionalization of aromatic amide with maleimide using *N*-substituted carboxamide as a directing group to obtain 3-arylated succinimides. Succinimides are important molecules that are featured in several natural products and commonly used medications. The succinimides can be easily reduced to pyrrolidines, lactims, or lactams, all of which are important motifs in several intermediates or natural products.[17] A robustness screen has been employed to describe the robustness and tolerance of the reaction.

EXPERIMENTAL SECTION

General Experimental Procedures. NMR spectra were recorded on a 400 MHz spectrometer in $CDCl_3$ or DMSO-d_6. Tetramethylsilane (TMS; δ = 0.00 ppm) for ^1H NMR in $CDCl_3$ and residual nondeuterated solvent peak (δ = 2.50 ppm) in DMSO-d_6 served as an

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internal standard. The solvent signal ($CDCl_3$, δ = 77.00 ppm; and DMSO-d_6, δ = 39.5 ppm) was used as an internal standard for ^{13}C NMR. IR spectra were measured using an FT-IR spectrometer. Mass spectra were obtained with a Q-TOF mass spectrometer (ESI-HRMS). Flash column chromatography was carried out by packing glass columns with commercial silica gel 230−400 mesh (commercial suppliers), and thin-layer chromatography was carried out using silica gel GF-254. All catalysts, reagents, and reactants were procured from commercial suppliers. Dichloroethane solvent was distilled over calcium hydride, stored over molecular sieves, and used for all procedures. Other solvents, used for workup and chromatographic procedures, were purchased from commercial suppliers and used without any further purification.

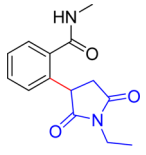
NMR Yield Calculations. After workup, 0.5 equiv of terephthaldehyde was added into the round-bottom flask containing the combined organic layers from the workup. Either an aliquot from the round-bottom flask was taken, evaporated, and then submitted for NMR or the organic layer was completely evaporated, and the residue was dissolved in an appropriate amount of solvent to submit for NMR.

Preparation of Amides. To a solution of benzoyl chloride (2.0 g, 14.23 mmol) in anhydrous Et_2O (25 mL) was added K_2CO_3 (4.92 g, 35.57 mmol) followed by $MeNH_3Cl$ (1.44 g, 21.34 mmol). The mixture was stirred at ambient temperature overnight, diluted with EtOAc (50 mL), and washed with H_2O (50 mL). The aqueous phase was extracted with EtOAc (2 × 30 mL), and the combined organic phase was dried over Na_2SO_4 and filtrated. The solvents were removed in vacuum to give a crude product, which was purified by column chromatography on silica gel (*n*-hexane/EtOAc 1/1) to yield *N*-methylbenzamide as a colorless solid (1.84 g, 96%).

Typical Procedure for Synthesis of 3aa. In an 8 mL screw cap reaction vial, 11.7 mg (20 mol %) $AgBF_4$ was weighed in and 9.2 mg (5 mol %) of $[Ru(p\text{-cymene})Cl_2]_2$ was added followed by the addition of 2 mL of DCE. Then both starting materials **1a** (40.5 mg, 0.3 mmol) and **2a** (56.3 mg, 0.45 mmol) were added, followed by the addition of $Cu(OAc)_2{\cdot}H_2O$ (90 mg, 0.45 mmol). To this mixture was added 0.17 mL (3.0 mmol) of AcOH, and the reaction vial was sealed with the screw cap and placed into a preheated metal block at 100 °C. The progress of the reaction was monitored by TLC.

Typical Procedure for Synthesis of 6aa. In na 8 mL screw cap reaction vial, 20.6 mg (20 mol %) of $AgSbF_6$ was weighed in and 9.2 mg (5 mol %) of $[Ru(p\text{-cymene})Cl_2]_2$ was added followed by the addition of 2 mL of DCE. Then both the starting materials **4a** (40.5 mg, 0.3 mmol) and **5a** (56.3 mg, 0.45 mmol) were added, followed by the addition of $Cu(OAc)_2{\cdot}H_2O$ (90 mg, 0.45 mmol). The reaction vial was sealed with the screw cap and placed into a preheated metal block at 80 °C. The progress of the reaction was monitored by TLC.

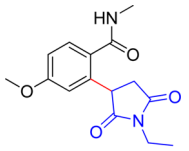
Experimental Data. *2-(1-Ethyl-2,5-dioxopyrrolidin-3-yl)-N-methylbenzamide (**3aa**).*



3aa

Prepared as described in the general procedure. The crude reaction mixture was purified on a silica gel column (hexane/EtOAc, 40:60) to obtain the product as pale yellow solid (mp = 75−78 °C); Yield = 71 mg (91%); R_f (50% EtOAc/hexane) 0.2; IR (neat, cm^{-1}) 3356, 1696, 1651, 1600; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 7.8 Hz, 1H), 7.41 (t, J = 7.7 Hz, 1H), 7.33 (t, J = 7.7 Hz, 2H), 6.7 (s, 1H), 4.38 (dd, J = 4.6 Hz, J = 9.3 Hz, 1H), 3.62 (q, J = 7.3 Hz, 2H), 3.18 (dd, J = 9.13 Hz, J = 18.26 Hz, 1H), 2.92−2.87(m, 4H), 1.22 (t, J = 7.53 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 178.5, 176.1, 169.7, 136.5, 135.3, 130.8, 128.2, 128.0, 128.0, 44.1, 37.7, 34.0, 26.7, 12.9; HRMS (ESI-TOF) (m/z) calcd for $C_{14}H_{16}N_2O_3Na$ (M + Na) 283.1059, found (M + Na) 283.1059.

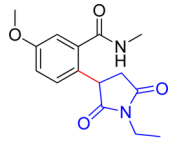
*2-(1-Ethyl-2,5-dioxopyrrolidin-3-yl)-4-methoxy-N-methylbenzamide (**3ba**).*



3ba

Prepared as described in the general procedure. The crude reaction mixture was purified on a silica gel column (hexane/EtOAc, 40:60) to obtain the product as a pale yellow liquid: yield = 75 mg (86%); R_f (40% EtOAc/hexane) 0.2; IR (neat, cm^{-1}) 3366, 2940, 1772, 1696, 1652; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.6 Hz, 1H), 6.80 (dd, J = 4.6 Hz, J = 8.6 Hz, 1H), 6.69 (s, 1H), 6.62 (d, J = 2.4 Hz, 1H), 4.38 (dd, J_1 = 4.6 Hz, J_2 = 9.4 Hz, 1H), 3.80 (s, 3H), 3.61 (q, J = 7.7 Hz, 2H), 3.16 (dd, J_1 = 9.1 Hz, J_2 = 18.2 Hz, 1H), 2.91−2.85 (m, 4H), 1.22 (t, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 178.3, 176.1, 169.4, 161.1, 137.5, 129.7, 128.4, 114.9, 112.2, 55.3, 44.3, 37.7, 33.9, 26.6, 12.8; HRMS (ESI-TOF) (m/z) calcd for $C_{15}H_{18}N_2O_4Na$ (M + Na) 313.1164, found (M + Na) 313.1169.

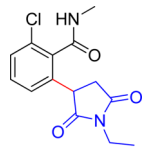
*2-(1-Ethyl-2,5-dioxopyrrolidin-3-yl)-5-methoxy-N-methylbenzamide (**3ca**).*



3ca

Prepared as described in the general procedure. The crude reaction mixture was purified on a silica gel column (hexane/EtOAc, 70:30) to obtain the product as a colorless liquid: yield = 35 mg (40%); R_f (50% EtOAc/hexane) 0.2; IR (neat, cm^{-1}) 3378, 1770, 1695, 1652; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.22 (t, J = 7.20 Hz, 4 H) 2.88 (dd, J_1 = 18.44, J_2 = 4.80 Hz, 1 H) 2.96 (d, J = 4.80 Hz, 3 H) 3.17 (dd, J_1 = 18.44, J_2 = 9.35 Hz 1 H) 3.62 (q, J = 7.07 Hz, 2 H) 3.82 (s, 3 H) 4.31 (dd, J_1 = 9.47, J_2 = 4.93 Hz, 1 H) 6.78 (br. s., 1 H) 6.91−6.97 (m, 1 H) 6.98−7.06 (m, 2 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.0, 176.2, 169.6, 159.0, 137.9, 129.0, 126.7, 116.6, 113.5, 55.5, 43.1, 37.6, 34.1, 26.8, 12.9; HRMS (ESI-TOF) (m/z) calcd for $C_{15}H_{18}N_2O_4Na$ (M + Na) 313.1164, found (M + Na) 313.1163.

*2-Chloro-6-(1-ethyl-2,5-dioxopyrrolidin-3-yl)-N-methylbenzamide (**3da**).*



3da

Prepared as described in the general procedure. The crude reaction mixture was purified on a silica gel column (hexane/EtOAc, 40:60) to obtain the product as a white solid (mp = 129−132 °C); yield = 81 mg (91%); R_f (50% EtOAc/hexane) 0.2; IR (neat, cm^{-1}) 3322, 1773, 1699, 1654; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 7.8 Hz, 1H), 7.31 (t, J = 7.7 Hz, 1H), 6.97 (d, J = 7.6 Hz, 1H), 6.58 (d, J = 3.8 Hz, 1H), 4.1 (dd, J_1 = 5.3 Hz, J_2 = 9.2 Hz, 1H), 3.60 (q, J = 7.8 Hz, 2H), 3.18 (dd, J_1 = 9.2 Hz, J_2 = 19.2 Hz, 1H), 3.0 (d, J = 4.9 Hz, 3H), 2.82 (dd, J_1 = 4.90 Hz, J_2 = 18.64 Hz, 1H), 1.12 (t, J = 7.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 177.4, 175.4, 166.8, 137.3, 136.6, 131.8, 130.6, 129.2, 124.7, 43.6, 37.2, 34.2, 26.5, 12.9; HRMS (ESI-TOF) (m/z) calcd for $C_{14}H_{15}ClN_2O_3Na$(M + Na) 317.0669, found (M + Na) 317.0665.

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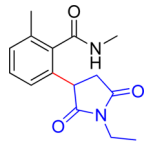
J. Org. Chem. 2016, 81, 6056−6065

*2-(1-Ethyl-2,5-dioxopyrrolidin-3-yl)-6-iodo-N-methylbenzamide (**3ea**).*

3ea

Prepared as described in the general procedure. The crude reaction mixture was purified on a silica gel column (hexane/EtOAc, 60:40) to obtain the product as a colorless liquid: yield = 79 mg (68%); R_f (50% EtOAc/hexane) 0.2; IR (neat, cm^{-1}) 3323, 1773, 1699, 1649; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 7.6 Hz, 1H), 7.07 (t, J = 7.9 Hz, 1H), 7.02 (d, J = 7.6 Hz, 1H), 6.5 (d, J = 4.0 Hz, 1H), 4.11 (dd, J_1 = 5.3 Hz, J_2 = 10.4 Hz, 1H), 3.6 (q, J = 7.5 Hz, 2H), 3.17 (dd, J_1 = 9.7 Hz, J_2 = 19.0 Hz, 1H), 3.01(d, J = 4.9 Hz, 3H), 2.79 (dd, J_1 = 4.81 Hz, J_2 = 18.66 Hz, 1H), 1.20 (t, J = 7.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, Few drops of DMSO-d_6 in $CDCl_3$) δ 176.8, 175.0, 169.1, 143.4, 138.0, 136.0, 130.4, 125.9, 93.7, 43.8, 37.3, 33.6, 26.0, 12.5; HRMS (ESI-TOF) (m/z) calcd for $C_{14}H_{15}IN_2O_3Na$ (M + Na) 409.0025, found (M + Na) 409.0023.

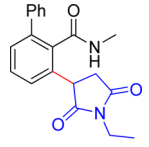
*2-(1-Ethyl-2,5-dioxopyrrolidin-3-yl)-N,6-dimethylbenzamide (**3fa**).*



3fa

Prepared as described in the general procedure. The crude reaction mixture was purified on a silica gel column (hexane/EtOAc, 70:30) to obtain the product as pale yellow liquid: yield = 42 mg (51%); R_f (50% EtOAc/hexane) 0.3; IR (neat, cm^{-1}) 3377, 1771, 1732, 1689; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, J = 7.17 Hz, 3 H) 2.33−2.45 (m, 3 H) 2.85 (dd, J_1 = 18.77, J_2 = 4.43 Hz, 1 H) 3.00 (d, J = 4.88 Hz, 3 H) 3.17 (dd, J_1 = 18.77, J_2 = 9.61 Hz, 1 H) 3.60 (q, J = 7.02 Hz, 2 H) 4.09 (dd, J_1 = 9.46,J_2 = 4.58 Hz, 1 H) 6.85 (d, J = 7.63 Hz, 1 H) 7.16 (d, J = 7.63 Hz, 1 H) 7.22−7.32 (m, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 178.4, 176.0, 169.8, 138.1, 136.0, 133.7, 129.9, 129.6, 122.8, 77.3, 77.0, 76.7, 43.1, 37.1, 34.1, 26.4, 19.6, 12.9; HRMS (ESI-TOF) (m/z) calcd for $C_{15}H_{18}N_2O_3Na$ (M + Na) 297.1215, found (M + Na) 297.1216.

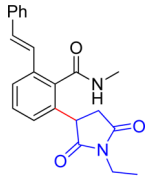
*3-(1-Ethyl-2,5-dioxopyrrolidin-3-yl)-N-methyl-[1,1′-biphenyl]-2-carboxamide (**3ga**).*



3ga

Prepared as described in the general procedure. The crude reaction mixture was purified on a silica gel column (hexane/EtOAc, 70:30) to obtain the product as white solid (mp = 184−187 °C); yield = 80 mg (79%); R_f (50% EtOAc/hexane) 0.4; IR (neat, cm^{-1}) 3376, 1772, 1733, 1696; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, J = 7.17 Hz, 4 H) 2.63 (d, J = 4.88 Hz, 3 H) 2.90 (dd, J_1 = 18.46, J_2 = 4.73 Hz, 1 H) 3.26 (dd, J= J_1 = 18.46, J_2 = 9.61 Hz, 1 H) 3.63 (q, J = 6.71 Hz, 2 H) 4.27 (dd, J_1 = 9.46, J_2 = 4.88 Hz 1 H) 5.70 (br. s., 1 H) 7.08 (d, J = 7.63 Hz, 1 H) 7.30−7.49 (m, 7 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 178.0, 176.0, 169.5, 140.4, 140.0, 136.7, 135.6, 130.0, 129.6, 128.5, 128.3, 128.0, 125.8, 77.3, 77.0, 76.7, 43.9, 38.0, 34.1, 26.4, 13.0; HRMS (ESI-TOF) (m/z) calcd for $C_{20}H_{20}N_2O_3Na$ (M + Na) 359.1372, found (M + Na) 359.1374.

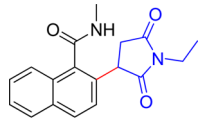
*(E)-2-(1-Ethyl-2,5-dioxopyrrolidin-3-yl)-N-methyl-6 styrylbenzamide (**3ha**).*



3ha

Prepared as described in the general procedure. The crude reaction mixture was purified on a silica gel column (hexane/EtOAc, 40:60) to obtain the product as yellow liquid; Yield = 71 mg (85%); R_f (50% EtOAc/hexane) 0.5; IR (neat, cm^{-1}) 3275, 1727, 1673, 1626; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18−1.25 (t, 3 H) 2.87 (dd, J= J_1 = 18.77, J_2 = 4.73 Hz, 1 H) 3.02 (d, J = 4.88 Hz, 3 H) 3.20 (dd, J_1 = 18.77, J_2 = 9.61 Hz 1 H) 3.62 (q, J = 7.12 Hz, 2 H) 4.15 (dd, J_1 = 9.46, J_2 = 4.58 Hz 1 H) 6.64 (d, J = 4.58 Hz, 1 H) 6.95 (d, J = 7.63 Hz, 1 H) 7.08 (d, J = 16.17 Hz, 1 H) 7.19 (d, J = 16.17 Hz, 1 H) 7.25−7.32 (m, 1 H) 7.37 (q, J = 7.73 Hz, 3 H) 7.49 (d, J = 7.32 Hz, 2 H) 7.65 (d, J = 7.93 Hz, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 178.2, 176.0, 169.35, 137.1, 136.8, 135.8, 134.6, 132.0, 130.0, 128.7, 128.1, 126.8, 125.2, 125.2, 124.8, 77.3, 77.0, 76.7, 43.3, 37.3, 34.2, 26.6, 13.00; HRMS (ESI-TOF) (m/z) calcd for $C_{22}H_{22}N_2O_3Na$ (M + Na) 385.1528, found (M + Na) 385.1530.

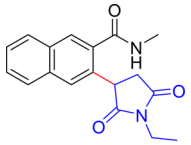
*2-(1-Ethyl-2,5-dioxopyrrolidin-3-yl)-N-methyl-1-naphthamide (**3ia**).*



3ia

Prepared as described in the general procedure. The crude reaction mixture was purified on a silica gel column (hexane/EtOAc, 70:30) to obtain the product as pale yellow solid (mp = 191−193 °C); Yield = 61 mg (65%); R_f (50% EtOAc/hexane) 0.3; IR (neat, cm^{-1}) 3359, 1772, 1734, 16952; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, J = 7.17 Hz, 3 H) 2.96 (dd, J J_1= 18.92, J_2 = 4.27 Hz 1 H) 3.11 (d, J = 4.88 Hz, 3 H) 3.25 (dd, J_1 = 18.92, J_2 = 4.46 Hz, 1 H) 3.64 (q, J = 7.32 Hz, 2 H) 4.34 (dd, J_1 = 9.46, J_2 = 4.27 Hz Hz, 1 H) 6.97 (br. s., 1 H) 7.07 (d, J = 8.55 Hz, 1 H) 7.46−7.60 (m, 2 H) 7.87 (d, J = 8.85 Hz, 1 H) 7.82 (d, J = 7.93 Hz, 1 H) 7.96 (d, J = 8.24 Hz, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 178.3, 176.0, 169.3, 132.6, 130.6, 130.2, 128.0, 127.7, 126.8, 125.5, 77.3, 77.0, 76.7, 43.4, 36.8, 34.3, 26.7, 13.00; HRMS (ESI-TOF) (m/z) calcd for $C_{18}H_{18}N_2O_3Na$ (M + Na) 333.1215, found (M + Na) 333.1213.

*3-(1-Ethyl-2,5-dioxopyrrolidin-3-yl)-N-methyl-2-naphthamide (**3ja**).*

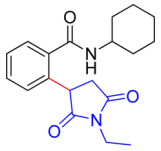


3ja

Prepared as described in the general procedure. The crude reaction mixture was purified on a silica gel column (hexane/EtOAc, 70:30) to obtain the product as pale yellow solid (mp = 200−202 °C); Yield = 77 mg (83%); R_f (50% EtOAc/hexane) 0.3; IR (neat, cm^{-1}) 3409, 1730, 1677, 1618; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J = 7.17 Hz, 3 H) 2.92−3.11 (m, 4 H) 3.24 (dd, J_1 = 18.16, J_2 = 9.31 Hz, 1 H) 3.66 (dd, J_1 = 7.17, J_2 = 1.97 Hz 2 H) 4.53 (dd, J_1 = 9.46, J_2 = 4.49 Hz 1 H) 7.49−7.59 (m, 2 H) 7.61 (s, 1 H) 7.75−7.81 (m, 1 H) 7.81−7.88 (m, 1 H) 8.01 (s, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 178.5, 176.2, 170.0, 133.8, 133.7, 132.4, 131.9, 128.4, 128.2, 128.0, 127.8, 127.4, 127.1, 77.3, 77.0, 76.7, 44.6, 38.0, 34.1, 26.8, 12.9; HRMS (ESI-TOF) (m/z) calcd for $C_{18}H_{18}N_2O_3Na$ (M + Na) 333.1215, found (M + Na) 333.1214.

DOI: 10.1021/acs.joc.6b01160
J. Org. Chem. 2016, 81, 6056−6065

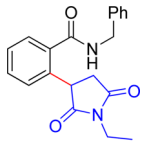
*N-Cyclohexyl-2-(1-ethyl-2,5-dioxopyrrolidin-3-yl)benzamide (**3ka**).*



3ka

Prepared as described in the general procedure. The crude reaction mixture was purified on a silica gel column (hexane/EtOAc, 50:50) to obtain the product as white solid (mp = 121−124 °C); Yield = 94 mg (95%); R_f (30% EtOAc/hexane) 0.3; IR (neat, cm^{-1})3326, 1774, 1698, 1645; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 7.7 Hz, 1H), 7.40 (t, J = 7.9 Hz, 1H), 7.32 (t, J = 8.0 Hz, 1H), 7.10 (d, J = 7.7 Hz, 1H), 6.60 (d, J = 6.7 Hz, 1H), 4.38 (dd, J_1 = 4.8 Hz, J_2 = 9.5 Hz, 1H), 3.93−3.85 (m, 1H), 3.60 (q, J = 7.7 Hz, 2H), 3.17 (dd, J_1 = 8.9 Hz, J_2 = 18.2 Hz, 1H), 2.87 (dd, J_1 = 5.0 Hz, J_2 = 18.5 Hz, 1H), 2.01−1.98 (m, 2H), 1.75−1.73 (m, 2H), 1.65−1.62 (m, 1H), 1.40 (m, 2H), 1.23−1.12 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 178.2, 176.0, 168.0, 136.9, 135.1, 130.6, 128.0, 127.9, 127.8, 48.8, 43.8, 37.6, 33.9, 33.0, 32.8, 25.4, 24.8, 24.7, 12.9; HRMS (ESI-TOF) (m/z) calcd for $C_{19}H_{24}N_2O_3Na$ (M + Na) 351.1685, found (M + Na) 351.1668.

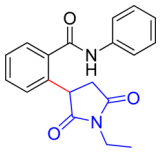
*N-Benzyl-2-(1-ethyl-2,5-dioxopyrrolidin-3-yl)benzamide (**3la**).*



3la

Prepared as described in the general procedure. The crude reaction mixture was purified on a silica gel column (hexane/EtOAc, 40:60) to obtain the product as white solid (mp = 112−115 °C); Yield = 88 mg (86%); R_f (50% EtOAc/hexane) 0.5; IR (neat, cm^{-1}) 3351, 1732, 1691, 1657; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, J = 7.32 Hz, 3 H) 2.85 (dd, J_1 = 18.31, J_2 = 5.49 Hz 1 H) 3.11 (dd, J_1 = 18.31, J_2 = 9.46 Hz 1 H) 3.51−3.64 (m, 2 H) 4.33 (dd, J_1 = 9.46, J_2 = 5.49 Hz 1 H) 4.53 (d, J = 5.80 Hz, 2 H) 7.03 (br. s., 1 H) 7.11 (d, J = 7.63 Hz, 1 H) 7.25−7.36 (m, 6 H) 7.37−7.44 (m, 1 H) 7.51 (d, J = 7.63 Hz, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 178.2, 176.0, 168.8, 137.9, 136.0, 135.5, 130.9, 128.7, 128.6, 128.0, 127.9, 127.7, 127.5, 77.3, 77.0, 76.7, 44.0, 43.9, 37.7, 33.9, 12.9; HRMS (ESI-TOF) (m/z) calcd for $C_{20}H_{20}N_2O_3Na$ (M + Na) 359.1372, found (M + Na) 359.1372.

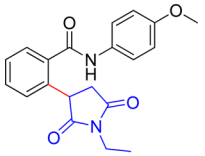
*2-(1-Ethyl-2,5-dioxopyrrolidin-3-yl)-N-phenylbenzamide (**3ma**).*



3ma

Prepared as described in the general procedure. The crude reaction mixture was purified on a silica gel column (hexane/EtOAc, 50:50) to obtain the product as pale yellow liquid; Yield = 30 mg (31%); R_f (30% EtOAc/hexane) 0.3; IR (neat, cm^{-1}) 3327, 1775, 1694, 1599; ^1H NMR (400 MHz, $CDCl_3$) δ 8.8 (s, 1H), 7.68 (d, J = 8.0 Hz, 3H), 7.47 (t, J = 7.35 Hz, 1H), 7.41 (t, J = 7.35 Hz, 1H), 7.35(t, J = 7.5 Hz, 2H), 7.16−7.13(m, 2H), 4.47 (dd, J_1 = 4.65 Hz, J_2 = 9.5 Hz, 1H), 3.61 (q, J = 7.50 Hz, 2H), 3.19 (dd, J_1 = 8.44 Hz, J_2 = 18.83 Hz, 1H), 2.94 (dd, J_1 = 4.7 Hz, J_2 = 18.6 Hz, 1H), 1.18 (t, J = 7.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 178.9, 175.9, 167.0, 138.0, 137.5, 134.5, 131.2, 129.0, 128.7, 128.3, 127.2, 124.6, 119.8, 43.4, 37.3, 34.2, 12.9; HRMS (ESI-TOF) (m/z) calcd for $C_{19}H_{18}N_2O_3Na$ (M + Na) 345.1215, found (M + Na) 345.1215.

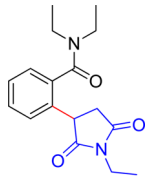
*2-(1-Ethyl-2,5-dioxopyrrolidin-3-yl)-N-(4-methoxyphenyl)-benzamide (**3na**).*



3na

Prepared as described in the general procedure. The crude reaction mixture was purified on a silica gel column (hexane/EtOAc, 50:50) to obtain the product as black solid (mp = 163−167 °C); Yield = 84 mg (79%); R_f (50% EtOAc/hexane) 0.3; IR (neat, cm^{-1}) 3320, 1773, 1697, 1601; ^1H NMR (400 MHz, $CDCl_3$) δ 8.84 (s,1H), 7.62 (d, J = 7.7 Hz,1H), 7.55 (d, J = 8.9 Hz, 2H), 7.42 (t, J = 8.0 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.17(d, J = 7.7 Hz, 1H), 6.85(d, J = 8.85 Hz, 2H), 4.41 (dd, J_1 = 4.75 Hz, J_2 = 9.56 Hz, 1H), 3.78(s,3H), 3.57 (q, J = 7.7 Hz, 2H), 3.13 (dd, J_1 = 9.15 Hz, J_2 = 18.30 Hz, 1H), 2.87 (dd, J_1 = 4.69 Hz, J_2 = 18.44 Hz, 1H), 1.16(t, J = 7.84 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 178.8, 176.0, 168.8, 156.5, 137.2, 134.8, 131.3, 131.0, 128.6, 128.1, 127.6, 121.6, 114.1, 55.5, 43.6, 37.4, 34.1, 12.9; HRMS (ESI-TOF) (m/z) calcd for $C_{20}H_{20}N_2O_4Na$ (M + Na) 375.1321, found (M + Na) 375.1318.

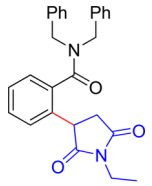
*N,N-Diethyl-2-(1-ethyl-2,5-dioxopyrrolidin-3-yl)benzamide (**3oa**).*



3oa

Prepared as described in the general procedure. The crude reaction mixture was purified on a silica gel column (hexane/EtOAc, 40:60) to obtain the product as pale yellow liquid: yield = 42 mg (51%); R_f (50% EtOAc/hexane) 0.2; IR (neat, cm^{-1}) 2978, 2939, 1774, 1703, 1625; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (t, J = 8.6 Hz, 1H), 7.32 (t, J = 7.3 Hz, 1H), 7.26 (t, J = 8.5 Hz, 1H), 7.11 (d, J = 7.5 Hz, 1H), 4.1 (dd, J = 4.9 Hz, J = 9.6 Hz, 1H), 3.63 (dd, J_1 = 8.6 Hz, J_2 = 16.7 Hz, 3H), 3.47 (m,1H), 3.29 (dd, J_1 = 8.5 Hz, J_2 = 16.9 Hz, 2H), 3.18 (dd, J_1 = 8.7 Hz, J_2 = 18.7 Hz, 1H), 2.82 (d, J = 17.0 Hz, 1H), 1.24 (q, J = 8.4 Hz, 6H), 1.14 (t, J = 8.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 177.7, 176.1, 170.2, 135.1, 129.7, 127.5, 126.3, 43.4, 39.0, 38.0, 33.9, 13.8, 13.0, 12.8; HRMS (ESI-TOF) (m/z) calcd for $C_{17}H_{22}N_2O_3Na$ (M + Na) 325.1528, found (M + Na) 325.1524.

*N,N-Dibenzyl-2-(1-ethyl-2,5-dioxopyrrolidin-3-yl)benzamide (**3pa**).*



3pa

Prepared as described in the general procedure. The crude reaction mixture was purified on a silica gel column (hexane/EtOAc, 30:70) to obtain the product as yellow liquid: yield = 92 mg (72%); R_f (50% EtOAc/hexane) 0.6; IR (neat, cm^{-1}) 3436, 1776, 1702, 1630; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.23 (t, J = 7.17 Hz, 3 H) 2.75 (dd, J_1 = 18.46, J_2 = 5.34 Hz 1 H) 3.05−3.27 (m, 1 H) 3.56−3.68 (m, 2 H) 4.15 (dd, J_1 = 9.46, J_2 = 5.19 Hz 1 H) 4.36−4.57 (m, 3 H) 4.93 (d, J = 14.04 Hz, 1 H) 7.11 (d, J = 7.63 Hz, 1 H) 7.20 (d, J = 7.02 Hz, 2 H) 7.23−7.43 (m, 12 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 177.5, 175.9, 170.8, 136.7, 135.9, 135.7, 130.1, 128.8, 128.6, 128.4, 127.7, 127.6, 127.6, 127.4, 126.3, 77.3, 77.0, 76.7, 51.9, 46.9, 43.3, 38.0, 34.0, 13.0; HRMS (ESI-TOF) (m/z) calcd for $C_{27}H_{26}N_2O_3Na$ (M + Na) 449.1841, found (M + Na) 449.1843.

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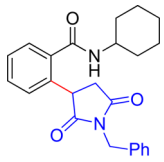
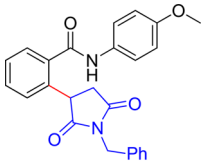
*2-(1-Benzyl-2,5-dioxopyrrolidin-3-yl)-N-cyclohexylbenzamide (**3kb**).*



3kb

Prepared as described in the general procedure. The crude reaction mixture was purified on a silica gel column (hexane/EtOAc, 40:60) to obtain the product as a white solid (mp = 156−159 °C): yield = 113 mg (96%); R_f (50% EtOAc/hexane) 0.5; IR (neat, cm^{-1}) 3348, 1760, 1688, 1629; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.13−1.32 (m, 4 H) 1.32−1.49 (m, 2 H) 1.56−1.67 (m, 2 H) 1.67−1.79 (m, 2 H) 1.88−2.03 (m, 2 H) 2.91 (dd, J_1 = 18.44, J_2 = 5.05 Hz 1 H) 3.22 (dd, J_1 = 18.44, J_2 = 9.60 Hz 1 H) 3.77−3.99 (m, 1 H) 4.42 (dd, J_1 = 9.60, J_2 = 5.31 Hz, 1 H) 4.62−4.83 (m, 2 H) 6.50 (d, J = 7.58 Hz, 1 H) 6.97−7.09 (m, 1 H) 7.27−7.36 (m, 4 H) 7.36−7.42 (m, 3 H) 7.49 (dd, J_1 = 7.33, J_2 = 1.52 Hz, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 178.1, 175.8, 168.0, 137.1, 135.7, 134.8, 130.7, 128.6, 128.0, 127.9, 127.8, 77.3, 77.0, 76.7, 48.9, 43.8, 42.7, 37.6, 33.0, 32.9, 25.5, 24.8, 24.7; HRMS (ESI-TOF) (m/z) calcd for $C_{24}H_{26}N_2O_3Na$ (M + Na) 413.1841, found (M + Na) 413.1841.

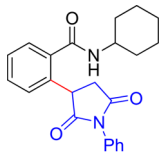
*2-(1-Benzyl-2,5-dioxopyrrolidin-3-yl)-N-(4-methoxyphenyl)-benzamide (**3nb**).*



3nb

Prepared as described in the general procedure. The crude reaction mixture was purified on a silica gel column (hexane/EtOAc, 70:30) to obtain the product as a blackish liquid: yield = 60 mg (48%); R_f (40% EtOAc/hexane) 0.7; IR (neat, cm^{-1}) 3322, 1774, 1699, 1664; ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (s,1H), 7.62 (d, J = 7.3 Hz,1H), 7.53 (d, J = 8.8 Hz, 2H), 7.40−7.25 (m, 7H), 7.04(d, J = 7.5 Hz, 1H), 6.86(d, J = 8.9 Hz, 2H), 4.68 (q, J = 8.1 Hz, 2H), 4.46 (dd, J_1 = 4.7 Hz, J_2 = 9.5 Hz, 1H), 3.79(s,3H), 3.18 (dd, J_1 = 8.3 Hz, J_2 = 18.7 Hz, 1H), 2.90 (dd, J_1 = 4.84 Hz, J_2 = 18.58 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 178.6, 175.7, 165.5, 137.3, 135.5, 134.5, 131.2, 131.0, 128.6, 128.6, 128.5, 128.2, 128.0, 127.3, 121.6, 114.1, 55.4, 43.5, 42.8, 37.3, 29.6; HRMS (ESI-TOF) (m/z) calcd for $C_{25}H_{22}N_2O_4Na$ (M + Na) 437.1477, found (M + Na) 437.1476.

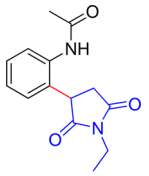
*N-Cyclohexyl-2-(2,5-dioxo-1-phenylpyrrolidin-3-yl)benzamide (**3kc**).*



3kc

Prepared as described in the general procedure. The crude reaction mixture was purified on a silica gel column (hexane/EtOAc, 30:70) to obtain the product as colorless liquid: yield = 53 mg (47%); R_f (50% EtOAc/hexane) 0.6; IR (neat, cm^{-1}) 3357, 1777, 1709, 1643; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.11−1.29 (m, 4 H) 1.31−1.41 (m, 2 H) 1.54−1.79 (m, 4 H) 1.88 (d, J = 11.12 Hz, 1 H) 1.94−2.03 (m, 1 H) 3.11 (dd, J_1 = 18.32, J_2 = 5.68 Hz 1 H) 3.32 (dd, J_1 = 18.32, J_2 = 9.73 Hz, 1 H) 3.89 (d, J = 8.34 Hz, 1 H) 4.47 (dd, 1 H J_1 = 9.60, J_2 = 5.81 Hz) 6.34 (d, J = 8.08 Hz, 1 H) 7.17−7.30 (m, 1 H) 7.30−7.54 (m, 8 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 177.3, 175.3, 168.3, 136.3, 135.3, 132.2, 130.8, 129.5, 129.1, 128.6, 128.1, 128.0, 126.8, 77.3, 77.0, 76.7, 48.9, 44.9, 38.0, 33.0, 32.9, 25.4, 24.9, 24.8; HRMS (ESI-TOF) (m/z) calcd for $C_{23}H_{24}N_2O_3Na$ (M + Na) 399.1685, found (M + Na) 399.1685.

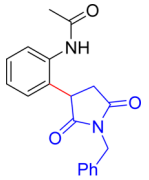
*N-(2-(1-Ethyl-2,5-dioxopyrrolidin-3-yl)phenyl)acetamide (**6aa**).*



6aa

Prepared as described in the general procedure. The crude reaction mixture was purified on a silica gel column (hexane/EtOAc, 30:70) to obtain the product as a pale colorless liquid: yield = 30 mg (38%); R_f (50% EtOAc/hexane) 0.1; IR (neat, cm^{-1}) 3281, 1773, 1698, 1523; ^1H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.52 (d, J = 7.5 Hz, 1H), 7.30 (t, J = 7.55 Hz, 1H), 7.21 (t, J = 7.7 Hz, 1H), 7.10 (d, J = 7.7 Hz, 1H), 4.29 (dd, J_1 = 4.7 Hz, J_2 = 9.4 Hz, 1H), 3.57 (q, J = 7.8 Hz, 2H), 3.09 (dd, J_1 = 9.44 Hz, J_2 = 18.76 Hz, 1H), 2.94(dd, J_1 = 4.4 Hz, J_2 = 18.65 Hz, 1H), 2.17 (s, 3H), 1.17 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 178.9, 175.8, 169.4, 136.1, 130.7, 128.4, 127.3, 126.6, 125.7, 41.2, 34.6, 34., 23.6, 12.8; HRMS (ESI-TOF) (m/z) calcd for $C_{14}H_{16}N_2O_3Na$ (M + Na) 283.1059, found (M + Na) 283.1059.

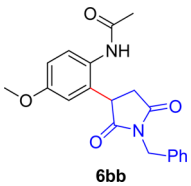
*N-(2-(1-Benzyl-2,5-dioxopyrrolidin-3-yl)phenyl)acetamide (**6ab**).*



6ab

Prepared as described in the general procedure. The crude reaction mixture was purified on a silica gel column (hexane/EtOAc, 40:60) to obtain the product as pale yellow liquid: yield = 40 mg (41%); R_f (50% EtOAc/hexane) 0.2; IR (neat, cm^{-1}) 3281, 1774, 1701, 1586; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.35 (d, J = 7.0 Hz, 2H), 7.32−7.29 (m,4H), 7.18 (t, J = 7.7 Hz, 1H), 7.06 (d, J = 7.7 Hz, 1H), 4.66(q, J = 15.2 Hz, 2H), 4.27 (dd, J_1 = 4.9 Hz, J_2 = 9.5 Hz, 1H), 3.09 (dd, J_1 = 4.4 Hz, J_2 = 18.8 Hz, 1H), 2.97(dd, J_1 = 97 Hz, J_2 = 18.9 Hz, 1H), 2.07 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 178.8, 175.6, 169.4, 136.1, 135.3, 130.3, 128.7, 128.7, 128.6,128.1, 128.1, 127.6, 126.7, 125.9, 42.7, 41.5, 34.5, 23.7; HRMS (ESI-TOF) (m/z) calcd for $C_{19}H_{19}N_2O_3$ (M + H) 323.1396, found (M + H) 323.1396.

*N-(2-(1-Benzyl-2,5-dioxopyrrolidin-3-yl)-4-methoxyphenyl)-acetamide (**6bb**).*



6bb

Prepared as described in the general procedure. The crude reaction mixture was purified on a silica gel column (hexane/EtOAc, 70:30) to obtain the product as colorless liquid: yield = 40 mg (38%); R_f (50% EtOAc/hexane) 0.2; IR (neat, cm^{-1}) 3271, 1774, 1701, 1657; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.01 (s, 3 H) 2.98 (dd, J J_1= 18.69, J_2 = 4.80 Hz 1 H) 3.12 (dd, J_1 = 18.69, J_2 = 9.35 Hz, 1 H) 3.74 (s, 3 H) 4.22 (dd, J_1 = 9.35, J_2 = 4.80 Hz, 1 H) 4.68 (q, J = 14.06 Hz, 2 H) 6.60 (d, J = 2.78 Hz, 1 H) 6.85 (dd, J = 8.84, 2.78 Hz, 1 H) 7.28−7.43 (m, 6 H) 7.79 (s, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 178.5, 175.5, 169.6, 158.3, 135.5, 132.7, 129.5, 128.9, 128.8, 128.6, 128.2, 113.4, 112.5, 55.5, 42.8, 42.1, 34.6, 23.5; HRMS (ESI-TOF) (m/z) calcd for $C_{20}H_{20}N_2O_4Na$ (M + Na) 375.1321, found (M + H) 375.1321.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01160.

^{1}H and ^{13}C NMR spectral data of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(3) This is based on the industrial bullion prices of the metals in both American and Asian markets. Ruthenium metal ($42/troy ounce) is about 14 times cheaper than palladium metal ($596/troy ounce). BASF Engelhard Industrial Bullion (EIB) Prices. http://apps.catalysts.basf.com/apps/eibprices/mp/ (accessed 17 May, 2016).

(4) Keyword searches on Google Scholar, "ruthenium catalyzed ortho" and "palladium catalyzed ortho" yield 29400 and 89100 hits, respectively (accessed 17 May, 2016).

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