C–H Activation

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Iterative C–H Functionalization Leading to Multiple Amidations of Anilides

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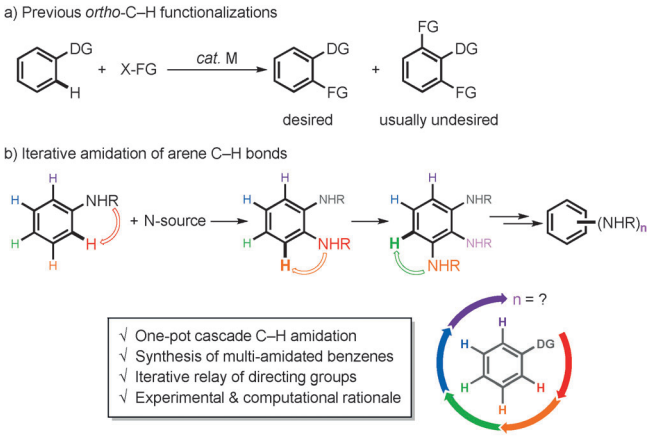
Abstract: *Polyaminobenzenes were synthesized by the ruthenium-catalyzed iterative C–H amidation of anilides using dioxazolones as an amino source. This strategy could be implemented by the sequential activation of C–H bonds of formerly generated compounds by cascade chelation assistance of newly installed amide groups. Computational studies provided a rationale.*

The demand for the selective synthesis of polysubstituted benzenes has increased because of their versatile utility in synthetic, medicinal, and materials chemistry.[1] In this context, two synthetic approaches can be conceived: 1) construction of a benzene skeleton with the simultaneous introduction of substituents, and 2) selective C–H functionalization of benzenes. In fact, various methods based on the former strategy are known, including [2+2+2][2] and [4+2] cycloaddition.[3]

Direct functionalization of benzenes is more attractive considering the availability of arene feedstocks.[4] While the chelation-assisted strategy has been remarkably successful for the single derivatization of chelation-group-containing arenes, double C–H functionalization is often nonselective and/or uncontrollable (Scheme 1 a).[5] Indeed, it is challenging to drive the C–H functionalization in one direction: either effective suppression of the second installation[6] or complete conversion to the double functionalization.[7] In this regard, we wondered about the feasibility of an iterative C–H functionalization of using a single mechanistic platform. For this goal, several issues can be considered: 1) can newly introduced functional groups work as an additional chelation unit to drive the subsequent C–H activation? and 2) how many iterations of C–H functionalization would proceed in one pot under the same catalyst system? (Scheme 1 b).

In continuing our efforts on the development of direct C–H amination reactions,[8] described herein is the realization of an iterative C–H amidation of anilides to afford multi-amidated benzenes. To the best of our knowledge, this is the first demonstration of an iterative one-pot C–H amidation of benzene derivatives. Computational studies provided a rationale on the extent of the cascade C–H amidation.



Scheme 1. Iterative C–H functionalization. DG = directing group, FG = functional group.

We have recently disclosed that 1,4,2-dioxazol-5-ones[9] can work as a highly efficient and robust amino source in transition metal catalyzed C–H amidation reactions.[10] This attractive feature of dioxazolones has been utilized subsequently by several research groups for the development of their own C–H amidation reactions.[11] We were intrigued by the use of anilides as a substrate[8b,10b,12] in a reaction with dioxazolones to lead to an iterative C–H amidation, based on a postulate that a newly installed amido group could also work as a directing group for subsequent and iterative C–N bond formations.

We commenced our study by examining several transition-metal catalysts in the C–H amidation of acetanilide to react with 1.1 equivalents of 3-phenyl-1,4,2-dioxazol-5-one (Table 1; see the Supporting Information for details). As we recently revealed,[10b] the cobalt precatalyst [{Cp*$CoCl_2$}$_2$], in combination with silver salts, was most efficient in this C–H amidation among group 9 metal congeners (entries 1–3). More significantly, a cationic ruthenium catalyst generated from [{Ru(*p*-cymene)Cl_2}$_2$] and $AgSbF_6$[13] exhibited notable efficiency (entry 4).

In our previous study of C–H amidation of anilides with dioxazolones,[10b] substituents in both reactants were found to be sensitive to the reaction efficiency. Therefore, various combinations of substrates and amidating precursors were examined. For this purpose, acetanilide (**1a**), *N*-phenylpivalamide (**1b**), and *N*-phenylbenzamide (**1c**) were reacted with a range of dioxazolone derivatives (**2a**, **2b** and **2c**; Table 1). The [Cp*Co^{III}] system did not exhibit notable reactivity in these amidation reactions (entries 5–7). We were pleased to

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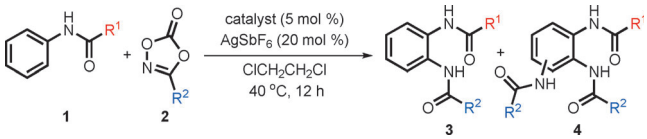
Table 1: Optimization studies.[a]



1 2 3 4

Entry	Catalyst	R^1	R^2	Yield [%][b]	
1	[{CoCp*Cl_2}$_2$]	Me	Ph	44 (**3a**)	<1 (**4a**)
2	[{RhCp*Cl_2}$_2$]	Me	Ph	<1 (**3a**)	<1 (**4a**)
3	[{IrCp*Cl_2}$_2$]	Me	Ph	31 (**3a**)	<1 (**4a**)
4	[{Ru(*p*-cymene)Cl_2}$_2$]	Me	Ph	51 (**3a**)	<1 (**4a**)
5	[{CoCp*Cl_2}$_2$]	Me	Me	20 (**3b**)	<1 (**4b**)
6	[{CoCp*Cl_2}$_2$]	*t*Bu	*t*Bu	<1 (**3c**)	<1 (**4c**)
7	[{CoCp*Cl_2}$_2$]	Ph	Ph	22 (**3d**)	<1 (**4d**)
8	[{Ru(*p*-cymene)Cl_2}$_2$]	Me	Me	12 (**3b**)	<1 (**4b**)
9[c]	[{Ru(*p*-cymene)Cl_2}$_2$]	*t*Bu	*t*Bu	52 (**3c**)	17 (**4c**)
10	[{Ru(*p*-cymene)Cl_2}$_2$]	Ph	Ph	<5 (**3d**)	<1 (**4d**)

[a] **1** (0.2 mmol), **2** (1.1 equiv), catalyst, and additive in $ClCH_2CH_2Cl$ (0.5 mL). [b] Determined by ^{1}H NMR analysis of the crude reaction mixture (internal standard: dibromomethane). [c] Tris-amidated product **5c** was also obtained (6%). Cp* = C_5Me_5.

observe that the reactivity was greatly improved when **1b** was employed under the ruthenium catalysis conditions. Indeed, almost full conversion of **2b** was achieved in the amidation of **1b** (entry 9). Moreover, noticeable amounts of bis-amidation (**4c**, 17%) and tris-amidation (**5c**, 6%) took place. The C–H amidation of either **1a** or **1c** with dioxazolones resulted in low efficiencies (entries 8 and 10).

Taking this pattern into consideration, it was concluded that the amidation of **1b** with **2b** is the best combination to furnish the C–H amidated products (**3c**, **4c**, and **5c**) under the ruthenium-catalyzed conditions at 40 °C. Moreover, the formation of a multi-amidated product, even using 1.1 equivalents of amidating reagent, led us to anticipate that multiple amidations would indeed be possible when larger amounts of the amino source are employed.

The structure of **3c** was confirmed by an X-ray crystallographic analysis (Figure 1a).[17] Two amide groups form an intramolecular hydrogen bond (H-bond) with one carbonyl oxygen pointing towards the N–H bond of the other amide group. Moreover, a structural analysis of **3c** by density functional theory (DFT) calculations revealed that another carbonyl oxygen is closely located in the direction of the *ortho*-C–H bond (2.3 Å between O1 and H1 in Figure 1a) in solution phase. This observation provides insight that the subsequent C–H activation of **3c** would be highly plausible, thus eventually enabling the iterative amidation. Pivaloyl groups of **3c** were readily removed upon acidic hydrolysis to afford 1,2-phenylenediamine in satisfactory yield (Figure 1b).

The influence of the H-bond on the subsequent C–H bond activation was next investigated (Figure 1c). We previously elucidated, in rhodium-catalyzed C–H amidation with organic azides, that a substrate works as a proton source in the final concerted metalation-deprotonation (CMD) step to deliver the amidated product with the regeneration of a cyclometalated complex.[8a] By analogy, a cationic ruthenium species, $[LRu\text{-}X]^+$, was postulated in the present amidation to be responsible for the formation of the ruthenacycle **A-3c** by a second C–H activation of **3c**, where L is *p*-cymene and X is deprotonated **3c** in an anionic amido form. Extended calculations on the CMD step from **3c** to **A-3c** revealed that the TS-CMD with H-bond is energetically favored by 2.4 kcal mol^{-1} when compared to that without having such H-bond. This result suggests that an intramolecular H-bond is maintained to drive the ruthenium-mediated C–H bond activation more favorably.

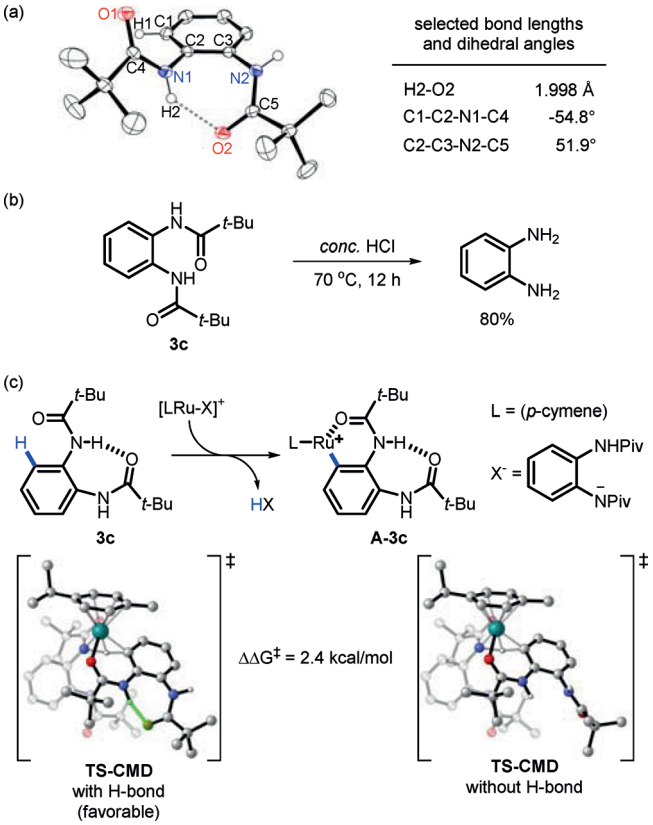


Figure 1. a) ORTEP of **3c** with selected bond lengths and angles. Thermal ellipsoids shown at 50% probability level (solvent molecules and several hydrogen atoms are omitted for clarity). b) Removal of pivaloyl groups of **3c**. c) C–H Bond activation process of **3c** in the presence and absence of H-bond.

We were pleased to observe that the desired iterative amidation indeed took place by using more equivalents of the dioxazolone in a reaction with **1b** (Figure 2). For instance, an almost equal ratio of tris-amidation (**5c**, 36%) and tetra-amidation (**6c**, 31%) was observed with the concomitant decrease in mono-amidation (**3c**, 19%) and bis-amidation (**4c**, 13%) when 3.1 equivalents of **2b** were employed. Finally, a quantitative formation of **6c** was observed when 6.1 or more equivalents of **2b** were applied. Interestingly, the last C–H bond of **6c** was not reacted even when larger amounts of **2b** (>8 equiv) were employed at 80 °C. This result suggests that the amidation of the last C–H bond in **6c** is intrinsically difficult to proceed under the present ruthenium catalysis (see below).

The structures of **4c** and **6c** were confirmed by X-ray crystallographic analyses (Figure 3).[17] These compounds also show intramolecular H-bonds between the neighboring amide groups.

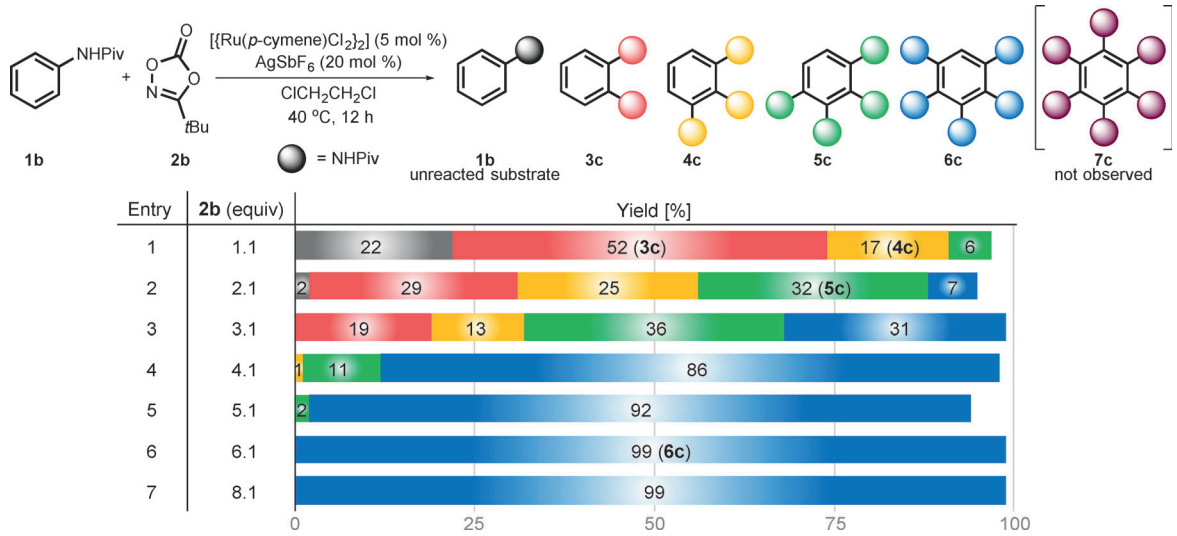


Figure 2. Synthesis of polyamidobenzenes. Conditions: **1b** (0.1 mmol), **2b**, catalyst, and additive in $ClCH_2CH_2Cl$ (0.5 mL). Yields were determined by ^1H NMR analysis of the crude reaction mixture (internal standard: dibromomethane).

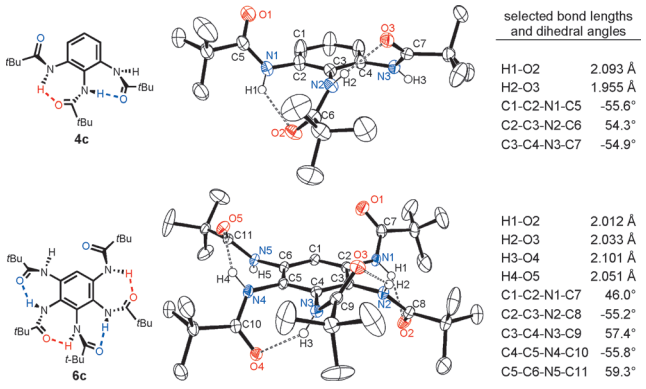
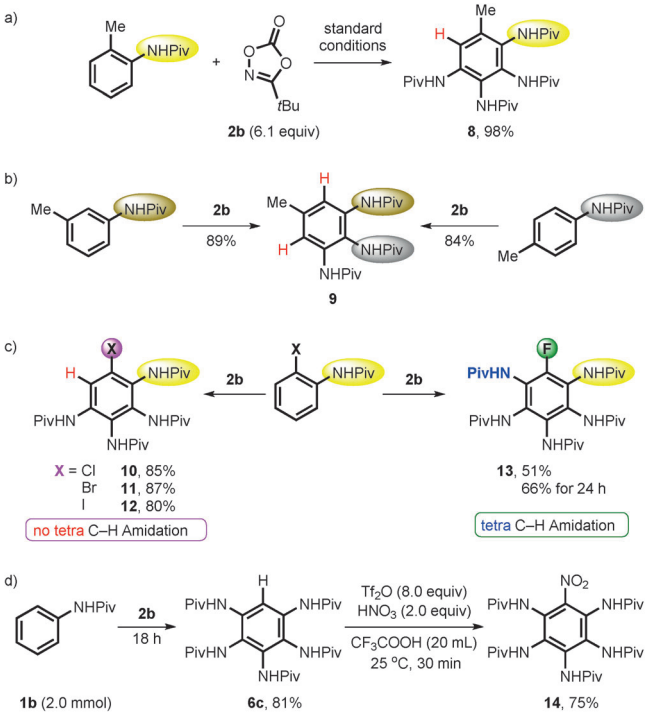


Figure 3. ORTEP of **4c** and **6c** with selected bond lengths and angles. Thermal ellipsoid shown at 50% probability level (solvent molecules and several hydrogen atoms are omitted for clarity).



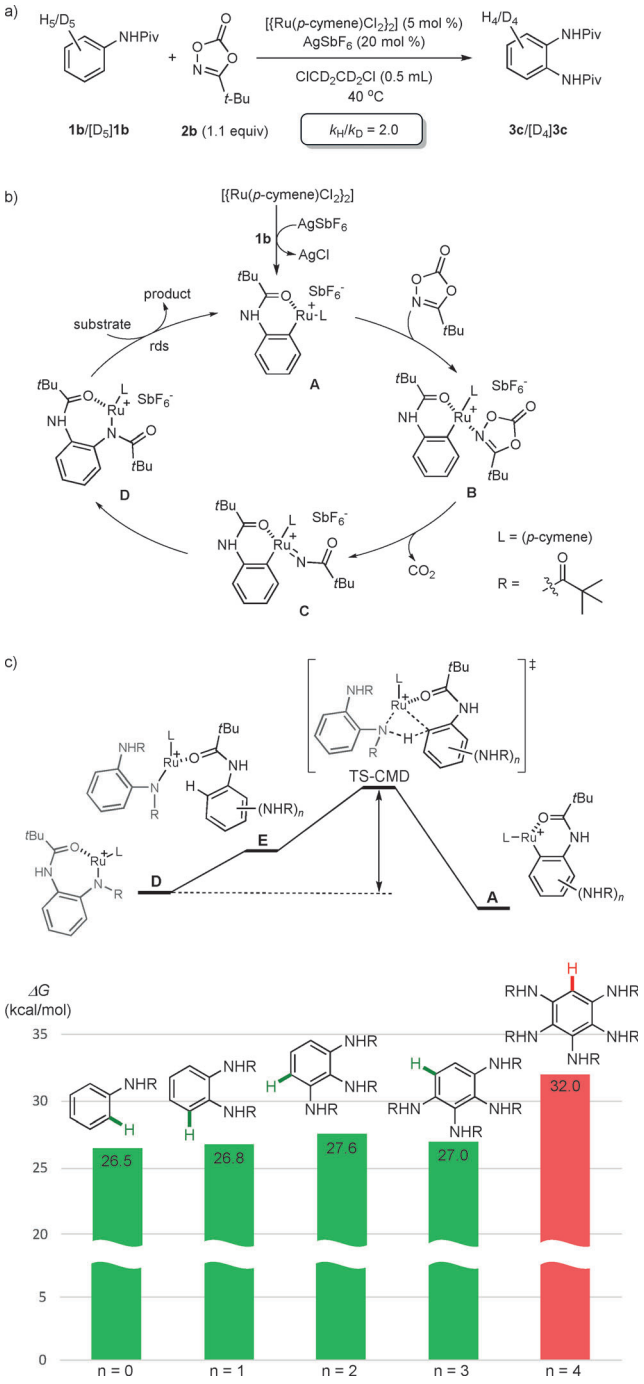
Scheme 2. Iterative C–H amidation of various anilides. Piv = pivaloyl, Tf = trifluoromethanesulfonyl.

The present iterative C–H amidation was applied to additional types of substrates (Scheme 2). When *N*-(*o*-tolyl)-pivalamide was subjected to reaction with **2b** (6.1 equiv), the tris-amidated product **8** was obtained in excellent yield (Scheme 2a). Again, the last C–H bond (*ortho* to methyl group) remained completely unreacted. A reaction of *N*-(*m*-tolyl)pivalamide gave the bis-amidated compound **9** exclusively, thus leaving two C–H bonds, *ortho* to the methyl substituent, intact (Scheme 2b). Interestingly, the same product **9** could also be obtained from *N*-(*p*-tolyl)pivalamide.

When anilide derivatives bearing *ortho* halides were reacted with **2b**, the extent of multiple C–H amidation was varied depending on the halide groups present (Scheme 2c). Tris-amidated products were formed exclusively from anilides having chloro, bromo, or iodo groups (**10**, **11**, and **12**). In sharp contrast, 2-fluoroanilide underwent the iterative C–H amidation exhaustively to furnish the tetra-amidated product **13** (Scheme 2c, right). This reaction result strongly suggests that the amidation at the last C–H bond is sensitive to steric factors.

The iterative C–H amidation was convenient on even gram scale (Scheme 2d). Significantly, nitration of **6c** at the last C–H bond was smooth and afforded pentaamidonitrobenzene (**14**) in good yield. It should be mentioned that since hexaaminobenzenes are an important structural unit in materials science,[14] preparative synthetic routes are highly desirable.[15]

To gain further mechanistic insight, a kinetic isotope effect (KIE) study was performed (Scheme 3a). A significant KIE value ($k_H/k_D = 2.0$) was measured, thus implying that the C–H bond cleavage is rate limiting. Given the present reactivity pattern in addition to the previous mechanistic studies,[10,13a,16] a plausible catalytic cycle is presented in Scheme 3b. First, a cationic ruthenium species induces the C–H activation to deliver the ruthenacycle **A**, where a dioxazolone will be coordinated and lead to **B**. A Ru^{IV}-imido species (**C**) is then assumed to form upon the oxidative CO_2 extrusion from **B**. Subsequent migratory insertion of an imido moiety will lead to the 7-membered ruthenacycle **D**. Finally, protodemetalation will take place by a CMD process by the interaction of **D** with an anilide substrate to release an amidated product with the regeneration of **A**.



Scheme 3. Mechanistic aspects of the iterative amidation.

Computational calculations for the proposed catalytic cycle on the formation of **3c** from **1b** with **2b** were performed (see the Supporting Information for details). The C–H bond activation of **1b** by **D** was calculated to have a barrier of 26.5 kcal mol^{-1} to regenerate the ruthenacycle **A** ($n = 0$; Scheme 3c). In addition, those in the subsequent CMD of the second, third, and fourth C–H bond activation to give the corresponding ruthenacycles **A** ($n = 1$, 2, and 3) turned out to be similar (26.8, 27.6, and 27.0 kcal mol^{-1}). This result implies that the cascade C–H amidation occurs with similar efficiency up to the fourth amidation. However, the fifth C–H activation barrier of **6c** (32.0 kcal mol^{-1}) was 4–5 kcal mol^{-1} higher than those of the first to fourth CMD processes. Again, this result is in a good agreement with the experimental observations that the amidation at the last C–H bond did not proceed under the present reaction conditions.

In conclusion, we have proven that a cascade C–H functionalization is highly feasible by developing an iterative ruthenium-catalyzed C–H amidation of anilides in reaction with dioxazolone amidating reagents. In this process, a newly introduced amide serves as an effective directing group for the successive C–H bond activation with the help of intramolecular H-bonds. DFT calculations and mechanistic studies rationalized the extent of the present cascade C–H amidation reactions. It showcases for the first time that an iterative C–H functionalization can be a powerful tool for introducing multiple functional groups in one-pot cascade manner.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: amidation · arenes · C–H activation · reaction mechanisms · ruthenium

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[17] CCDC 1526694 (**3c**), 1526695 (**4c**), and 1526696 (**6c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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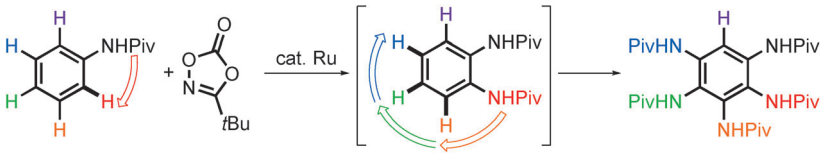
Communications

C–H Activation

J. Park, J. Lee, S. Chang* ▬▬–▬▬

Iterative C–H Functionalization Leading to Multiple Amidations of Anilides



Repeat performance: A ruthenium-catalyzed cascade amidation of multiple C–H bonds of anilide has been developed. By using dioxazolone as amidating reagents, newly installed amide groups serve as an additional directing groups to drive subsequent C–H activation. This reaction provides a simple and mild approach to the preparation of polyaminobenzenes.