Reaction Mechanisms

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# Product-Derived Bimetallic Palladium Complex Catalyzes Direct Carbonylation of Sulfonylazides

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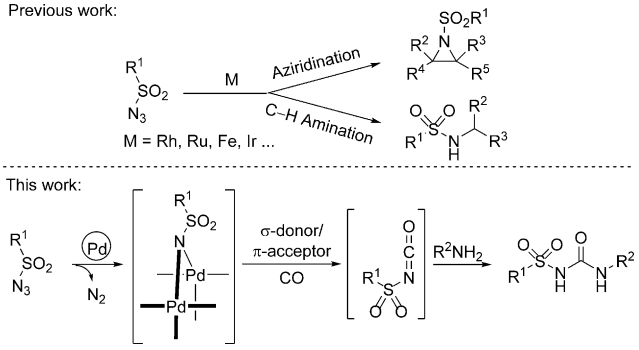
***Abstract:*** *A novel product-derived bimetallic palladium complex catalyzes a sulfonylazide-transfer reaction with the σ-donor/π-acceptor ligand CO, and is advantageous given its broad substrate scope, high efficiency, and mild reaction conditions (atmospheric pressure of CO at room temperature). This methodology provides a new approach to sulfonylureas, which are present in both pharmaceuticals and agrochemicals. The synthesis of Glibenclamide on a gram scale further revealed the practical utility of this procedure. Mechanistically, the generation of a bridged bimetallic palladium species derived from the product sulfonylurea is disclosed as the crucial step for this catalytic cycle.*

Selective transition-metal-catalyzed C–N bond formation via a nitrene has attracted considerable attention because of its high synthetic value in the construction of diverse N-containing compounds.[1] The recently developed procedure using organic azides as nitrene precursors does not require any external oxidant and releases $N_2$ as the only byproduct. In particular, commercially available and air-stable sulfonylazides have played an important role in achieving the concise synthesis of N-substituted sulfonyl amides. To date, these transformations are usually catalyzed by Rh, Ir, Ru, Fe, Co, etc.,[2] with either noble metals or complicated and sensitive ligands (Scheme 1). In contrast, palladium complexes, which serve as common catalysts for various cross-coupling reactions,[3] have rarely been used in the transformation of sulfonylazides. The palladium-catalyzed coupling reactions between carbenes/nitrenes with σ-donor/π-acceptor ligands, however, has grown remarkably in recent years. Palladium-catalyzed carbene-transfer reactions with CO, alkynes, and isocyanides to form ketenes, allenes, and ketenimines, respectively, have been well developed.[4] However, a direct palladium-catalyzed nitrene-transfer strategy with a σ-donor/π-acceptor ligand, which also represents a synthetically valuable method for introducing nitrogen moiety to unsaturated systems, has not been well explored.[5] To the best of our knowledge, palladium-catalyzed carbonylation of sulfonylazides has scarcely been reported. Thus, we have paid much attention to palladium-catalyzed cross-coupling reactions of sulfonylazides with CO, an approach which would provide a potential strategy to access sulfonyl isocyanate, a key intermediate to sulfonylurea derivatives.




***Scheme 1.*** A palladium-catalyzed carbonylation of sulfonylazides to synthesize sulfonylureas.

Sulfonylurea derivatives are common structural motifs in pharmaceuticals[6] and agrochemicals.[7] The traditional method to access sulfonylureas is the reaction of sulfamides with phenyl carbamates, and it produces much waste.[8] Other approaches include the coupling of either alkyl isocyanates with sulfamides,[9] or sulfonyl isocyanates with amines,[10] both of which require the use of phosgene. In addition, the former approach is unsatisfactory because of the weak nucleophilicity of sulfamides, whereas the latter approach is also limited because of the difficulty in synthesizing sulfonyl isocyanates. An alternative strategy to accessing sulfonyl isocyanates by transition-metal-catalyzed carbonylation of sulfonyl nitrenes has also been explored.[11] However, harsh reaction conditions, such as a high pressure of CO, substrate restrictions, and unavoidable formation of 1,3-disulfonylurea as a byproduct limit its application. Herein we describe a $Pd(OAc)_2$-catalyzed direct carbonylation of sulfonylazides under the atmospheric pressure of CO at room temperature, as well as tandem reactions with amines which afford sulfonylureas with unexpected excellent yields. Notably, mechanistic studies suggested that the sulfonylurea product itself serves as a ligand which bridges a bimetallic palladium species, thus forming the real catalyst in the transformation.

At the outset of our study, a reaction between $TsN_3$ (**1a**; Ts = 4-toluenesulfonyl) and morpholine (**2a**) was surveyed in the presence of 1 mol% $Pd(OAc)_2$ under a CO (1 atm) atmosphere in MeCN at room temperature. To our surprise, the sulfonylurea **3aa** was isolated in nearly quantitative yield. Further investigation of the reaction conditions[12] revealed that this reaction gives comparable yields in MeCN, THF, and PhMe, whereas high-polarity solvents such as DMF afforded poor yields. Comparison experiments showed that $Pd(OAc)_2$

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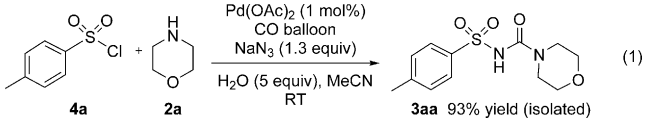
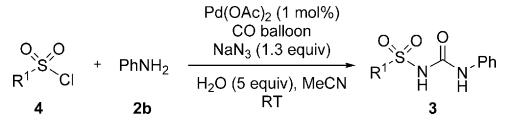
is the best catalyst. Furthermore, this carbonylation carried out directly from TsCl (**4a**) in a one-pot fashion also succeeded. After carefully optimizing the reaction conditions,[12] it was found that such a one-pot process could be achieved in up to 93% yield when 1.3 equivalents of $NaN_3$ was used and 5.0 equivalents of $H_2O$ was added [Eq. (1)].

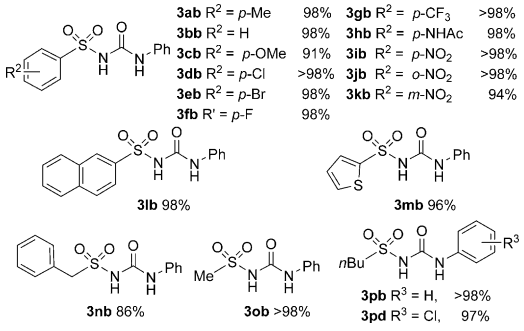



(1)

With the optimized reaction conditions in hand, the one-pot reaction to produce sulfonylureas were evaluated. First, an array of functionalized sulfonyl chlorides (**4**) with aniline (**2b**) was subjected to this reaction (Table 1). To our delight,

***Table 1:*** Substrate scope of the sulfonyl chlorides **4** and **2b**.[a]



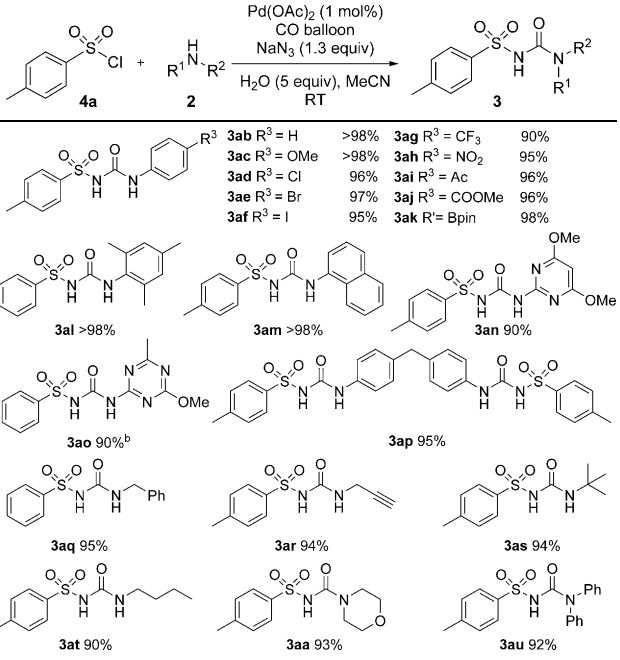




[a] Reaction conditions: **4** (0.4 mmol), **2b** (0.48 mmol), $Pd(OAc)_2$ (4 μmol), $NaN_3$ (0.52 mmol), $H_2O$ (5 equiv) in MeCN (4 mL) under CO balloon at room temperature. Yield of isolated products.

not only did aryl sulfonyl chlorides bearing an electron-withdrawing group give excellent results (**3gb**, **3ib**–**kb**), but those bearing an electron-donating group also gave greater than 90% yields (**3ab**,**cb**). The reactions with the sulfonyl chlorides bearing substituents at different positions of the aromatic ring all gave greater than 90% yields (**3ib**, **3jb,** and **3kb**). Importantly, halogen substituents were well-tolerated (**3db**–**fb**). Other arenes such as naphthalene and thiophene sulfonyl chlorides also worked very well (**3lb** and **3mb**). Finally, benzyl- and alkyl-substituted sulfonyl chlorides also gave greater than 85% yields (**3nb**–**pd**).

The scope with respect to the amines (**2**) was then examined (Table 2). Similarly, both electron-donating and electron-withdrawing substituents on the aniline ring gave mostly greater than 95% yields (**3ab**, **3ac**, **3ag**–**aj**). Halogenated amines, especially bromo- and iodo-substituted amines, which could easily undergo oxidative addition with a palladium species, gave 95–97% yields (**3ad**–**af**). Sterically hindered amines, such as 2,4,6-trimethylaniline (**3al**) and

***Table 2:*** Substrate scope of **4a** and the amines **2**.[a]



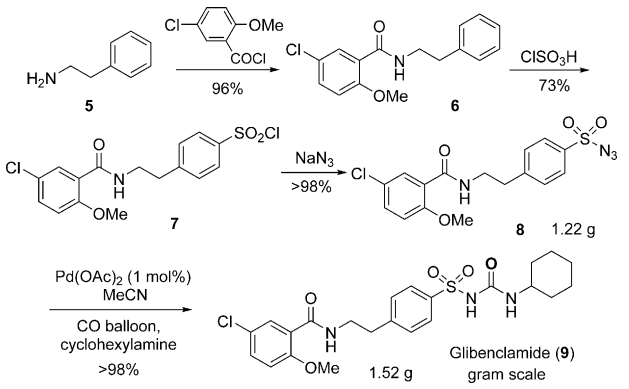

[a] Reaction conditions: **4a** (0.4 mmol), **2** (0.48 mmol), $Pd(OAc)_2$ (4 μmol), $NaN_3$ (0.52 mmol), $H_2O$ (5 equiv) in MeCN (4 mL) under CO balloon at room temperature. Yield of isolated product. [b] This reaction was carried out at 80 °C.

*t*$BuNH_2$ (**3as**), also led to greater than 98 and 94% yields, respectively. When amines were substituted by functional groups such as carbonyl (**3ai**), ester (**3aj**), alkynyl (**3ar**), even borate (**3ak**), the reaction yields were all above 94%. Notably, 4,6-dimethoxypyrimidin-2-amine (**3an**) and 4-ethyl-6-methoxy-1,3,5-triazin-2-amine (**3ao**), the core structure in most sulfonylurea herbicides,[7] both gave 90% yield. In addition, fused rings (**3am**), benzyl amines (**3aq**), alkyl amines (**3ar**–**3at**), secondary amines (**3aa**, **3au**), and diamines (**3ap**) all furnished greater than 90% yields.

Having revealed high efficiency to construct sulfonylureas, we assessed the potential of this reaction for synthesizing nitrogen-containing biologically active molecules in more complex scaffolds. The application of this strategy towards Glibenclamide (**9**), an antidiabetic drug, was investigated (Scheme 2). Starting from 2-phenylethanamine (**5**), Glibenclamide was synthesized in four steps and 70% overall yield. The key step, $Pd(OAc)_2$-catalyzed carbonylation of the sulfonylazide **8** with cyclohexylamine, has been studied on a gram scale, thus giving greater than 98% yield. Additionally, an alternative route which introduces the sulfonylazide group prior to building the benzoyl amide moiety also succeeded.[13]

With the unexpected excellent yields and splendid universality of this palladium-catalyzed sulfonylazide formation, mechanistic studies were performed to further understand the key factors. In previous reports, Besenyei and co-workers synthesized and characterized bimetallic palladium sulfonyl nitrenes ($[Pd_2Cl_2(dppm)_2(\mu\text{-}NSO_2Ar)]$) from $ArSO_2N_3$,[14] but further transformation had not been achieved. Nonetheless,

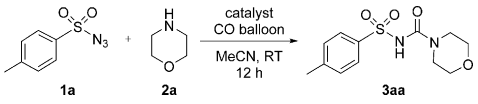



***Scheme 2.*** Synthesis of Glibenclamide.

based on their results and other reports about bimetallic nitrene complexes,[15] it is possible that a bridged bimetallic palladium species may be a part of this carbonylation process. $Pd(OAc)_2$, the best catalyst in our reaction, is also a common palladium species used in bimetallic $Pd^{II}$/hypervalent Pd catalytic cycles.[16]

Control experiments were carried out to compare the activity of different anions (Table 3). When $Pd(OAc)_2$ was used as the catalyst, or $PdCl_2$ with a NaOAc/AgOAc additive, the reactions all afforded excellent yields (entries 1 and 3).

***Table 3:*** Effect of different anion ligands.[a]




| Entry[a] | Cat. (5 mol%) | Additive (equiv) | Yield [%][b] |
|---|---|---|---|
| 1 | $Pd(OAc)_2$ | – | >98 |
| 2 | $PdCl_2$ | – | trace |
| 3 | $PdCl_2$ | NaOAc (0.1) or AgOAc (0.1) | >98 |
| 4 | $PdCl_2$ | PhCONH*n*Bu (0.1) | trace |
| 5 | $PdCl_2$ | TsNH*n*Bu (0.1) | 74 |
| 6 | $PdCl_2$ | Succinimide (0.1) | 64 |
| 7 | $PdCl_2$ | *o*-phthalimide (0.1) | 73 |
| 8 | $PdCl_2$ | $H_2L^1$[c] (0.1) | 85 |

[a] Reaction was carried out with 1.0 equiv of **1a**, and 1.2 equiv of **2a**. [b] Yields were determined by $^1H$ NMR spectroscopy using mesitylene as an internal standard. [c] $H_2L^1$ = *N*-(mesitylcarbamoyl)4-methylbenzenesulfonamide (**3al**).

However, $PdCl_2$ alone was found to be ineffective (entry 2). Besides an O,O-donor bridging ligand $OAc^-$, different types of N,O-donor and N,N-donor anions were further evaluated (entries 4–7). Normal amides, PhCONH*n*Bu, only gave trace product, while the sulfonylamide TsNH*n*Bu gave 74% yield. Succinimide and *o*-phthalimide are effective additives (entries 6 and 7). When the sulfonylurea product $H_2L^1$ (**3pd**) was used as the additive, the reactions also gave good yields (85%, entry 8). This observation suggests that the bridged bimetallic palladium species may be key to this transformation. It is also envisioned that the product sulfonylurea, which can serve as a bridging ligand, plays an important role.

To investigate the interaction of sulfonylurea and $Pd(OAc)_2$, HRMS studies of different mixtures of $Pd(OAc)_2$ with typical sulfonylureas were performed (see the Supporting Information for details). When sulfonylureas from a primary amine ($H_2L$) were used, the bimetal complexes $[Pd_2L^1{}_2(MeCN)_2]$ were observed. For example, $[Pd_2L^1{}_2(CH_3CN)_2H]^+$ was found (calculated: 957.07593, found: 957.07817) in the mixture of $Pd(OAc)_2$ with $H_2L^1$ in MeCN. Additionally, when performed in $[D_3]$MeCN, the corresponding $[Pd_2L^1{}_2(CD_3CN)_2H]^+$ could also be found (calculated: 963.11359, found: 963.11305). These results suggested that disulfonylurea bridged bimetallic palladium was the real active palladium species in the mixture.

Further NMR studies[17] also suggested that the acetate of $Pd(OAc)_2$ was replaced by $H_2L^1$. In Figure 1a, the shifts of $C_k$ and $C_l$ of acetate were $\delta = 20.8$ and 172.7 ppm, respectively, nearly the same as those of HOAc ($\delta = 20.8$ and 174.6 ppm),

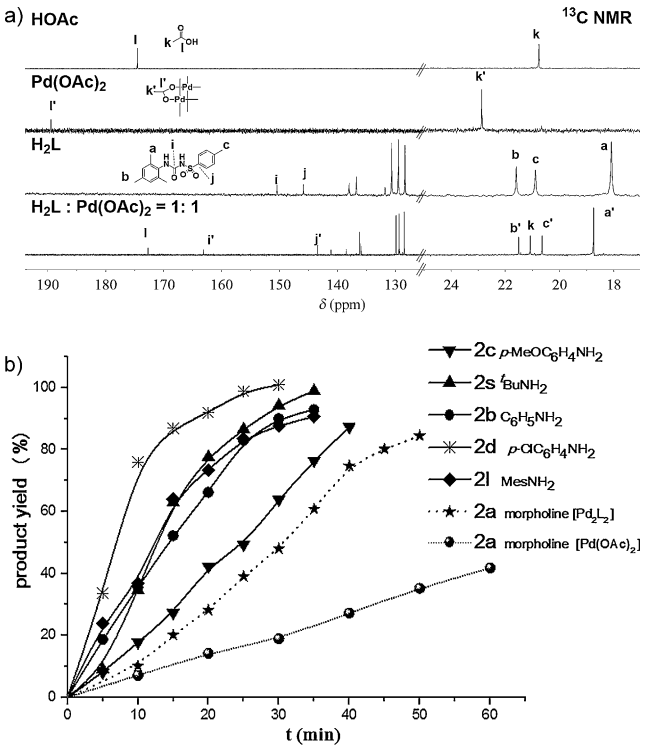
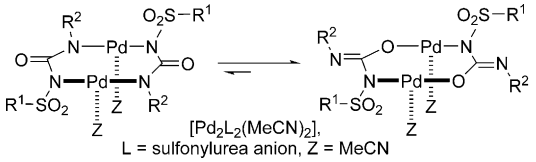



***Figure 1.*** a) $^{13}C$ NMR spectra of HOAc, $Pd(OAc)_2$, $H_2L^1$ (**3al**), and a 1:1 mixture of $H_2L^1$ (**3al**) and $Pd(OAc)_2$ in $[D_3]$MeCN at 25°C. b) Rate curve of the reactions between $TsN_3$ (**1a**) and different amines (**2**)and the reactions between **1a** and **2a** with either $Pd(OAc)_2$ or $[Pd_2L^1{}_2(CH_3CN)_2]$ as the catalyst.

but not $Pd(OAc)_2$ ($\delta = 22.8$ and 189.4 ppm). These results illustrate that acetate disassociates from the palladium center when $Pd(OAc)_2$ was mixed with $H_2L^1$. Notably, the signal of the sufonylurea carbonyl group, Ci′, in the $[Pd_2L^1{}_2(MeCN)_2]$ complex was $\delta = 163.2$ ppm, 13 ppm downfield from that of the signal of $H_2L^1$ ($\delta = 150.4$ ppm). Additionally, in the $^1H$ NMR study, the signal of the active protons of the sufonylurea disappeared upon mixing. It is another indication that the sulfonylurea bridged two palladium atoms. The

sulfonylurea-bridged palladium could be an N,O-donor form or an N,N-donor form, and the NMR analysis suggested that the N,O-donor form would be dominant [Eq. (2)].[17] How-



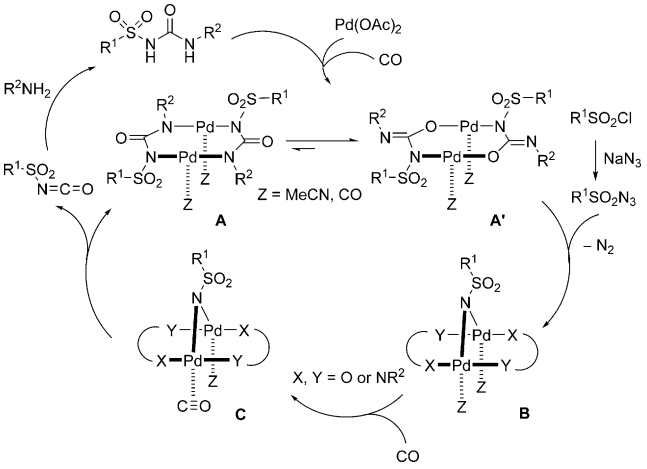

(2)

ever, for the sulfonylurea **3aa**, derived from the secondary amine morpholine (**2a**), the NMR spectrum of the mixture of sulfonylurea and $Pd(OAc)_2$ was no different from that of the free sulfonylurea. In addition, when mixing $Pd(OAc)_2$ with **3aa** and **3al** together, only the change of **3al** could be found (see the Supporting Information for details).

To further understand the role of the product sulfonylurea itself in the reactions, relative rates of the reactions between **1a** and different amines were studied (Figure 1b). Regardless of whether $PhNH_2$ (**2b**), *p*-$MeOC_6H_4NH_2$ (**2c**), *p*-$ClC_6H_4NH_2$ (**2d**), or $MesNH_2$ (**2l**) were used, the conversions were completed in 40 minutes. The rate of the reaction of bulky alkyl amine *t*$BuNH_2$ (**2s**) was also faster, up to 98% in 35 minutes. However, the reaction the secondary amine **2a** gave only 42% product after 1 hour, and required more than 1.5 hours to complete. These results do not accord with the nucleophilicity of different amines.[18] Together with the above investigation of the interaction of sulfonylurea and $Pd(OAc)_2$, one reasonable explanation was that the presence of different sulfonylurea products would affect the rate of TsNCO formation. Then we further studied relative rates of the reactions of **2a** with only $Pd(OAc)_2$ and using sulfonylurea $H_2L^1$ as the additive. Clearly, the reaction proceeded at a much quicker rate when the catalyst was changed from $Pd(OAc)_2$ to $[Pd_2L^1{}_2(MeCN)_2]$. It was complete in 40 minutes, the same as other reactions performed in Figure 1b. This data is important evidence that the sulfonylureas from primary amines are superior to the acetate ligand in terms of coordination to palladium, that this product-bridged palladium species, which has higher reactivity, is the real active catalyst in sulfonylazide carbonylation with primary amines.

Based on the above investigations and other reports of discrete late-metal nitrenes with CO to give isocyanates,[19] a possible reaction mechanism was proposed (Scheme 3). Initially, the in situ generated sulfonylurea product (from primary amines) combined with $Pd(OAc)_2$ in the presence of CO to produce a MeCN/CO-coordinated bimetallic palladium complex in the N,N-donor form **A**, or N,O-donor form **A′**, which was suggested as the real active catalyst in this reaction. Then, reaction of **A**/**A′** with the sulfonylazide took place along with dinitrogen extrusion to afford the bimetallic palladium nitrene complex **B**. Subsequently, insertion of the σ-donor/π-acceptor ligand CO into the palladium nitrene complex **C** to produce the sulfonyl isocyanate **D** with the regeneration of **A**/**A′**. Finally, nucleophilic addition of the amine component furnishes sulfonylurea as the final product.

In summary, we have developed a novel palladium-catalyzed nitrene-transfer reaction of sulfonylazides with




***Scheme 3.*** Proposed mechanism.

CO. The reactions are operationally simple and proceed smoothly under mild reaction conditions to afford highly functionalized sulfonylureas in outstanding yields, thus demonstrating broad applications in both pharmaceuticals and pesticides. The gram-scale preparation exhibited nearly quantitative yield, and the synthesis of Glibenclamide revealed the promising implementation of our methodology in total synthesis. In addition, mechanistic studies as well as NMR spectroscopy, HRMS, and control experiments provide evidence to support the presence of a bridging ligand as key to this reaction. Furthermore, the bimetallic palladium species derived from the product sulfonylurea is superior to $Pd(OAc)_2$, and is the real active catalyst during the carbonylation. This work amply demonstrates that palladium-catalyzed reactions of sulfonylazides show great potential in the synthesis of functionalized nitrogen-containing compounds, and bridged bimetallic palladium species may play an important role for palladium nitrene generation from sulfonylazides.

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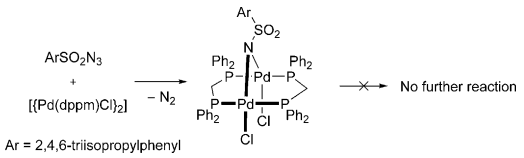
[12] For more details, see the Tables S2–S4 in the Supporting Information.

[13] For more details about another route in which 4-(2-aminoethyl) benzenesulfonyl azide (**13**) was synthesized first, a convenient way to diversity of the benzoyl amide moiety. See Scheme S1 Route 2 in the Supporting Information.

[14] a) G. Besenyei, L. Parkanyi, I. Foch, L. I. Simándi, A. Kalman, *Chem. Commun.* **1997**, 1143 – 1144; b) G. Besenyei, L. Parkanyi, I. Foch, L. I. Simándi, A. Kalman, *Angew. Chem. Int. Ed.* **2000**, *39*, 956 – 958; *Angew. Chem.* **2000**, *112*, 986 – 988.

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[17] According to D. C. Powers, D. Y. Xiao, M. A. L. Geibel, T. Ritter, *J. Am. Chem. Soc.* **2010**, *132*, 14530 – 14536, the acetate carbonyl $^{13}C$ signal of the acetate-bridged palladium dimer was around $\delta = 185$ ppm, 8 ppm downfield relative to that of single-chelating acetate ligand. The succinate carbonyl $^{13}C$ signal of a succinate-bridged palladium dimer was around $\delta = 190$ ppm, also about 10 ppm downfield from that of singly chelated succinate ligand. For more details, see the Supporting Information.

[18] p$K_a$ of morpholine (**2a**) is 8.36, p$K_a$ of $PhNH_2$ (**2b**) is 4.62, p$K_a$ of *p*-$MeOC_6H_4NH_2$ (**2c**) is 5.29, p$K_a$ of *p*-$ClC_6H_4NH_2$ (**2d**) is 3.81, p$K_a$ of $MesNH_2$ (**2l**) is 4.74, p$K_a$ of $^tBuNH_2$ (**2s**) is 10.55. For reference, see: H. K. Hall, Jr., *J. Am. Chem. Soc.* **1957**, *79*, 5441 – 5444.

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