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Palladium Nanoparticle-Catalyzed Direct Ethynylation of Aliphatic Carboxylic Acid Derivatives *via* C(sp^3)–H Bond Functionalization

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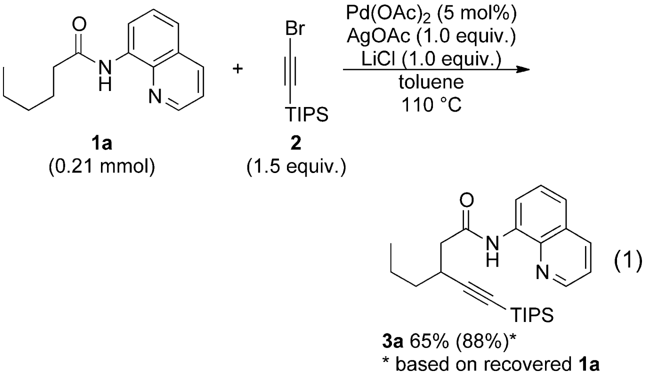
Abstract: We have developed a sulfur-modified, gold-supported palladium material (SAuPd) with palladium, Pd, nanoparticles on its surface; it is a recyclable, low-leaching Pd catalyst. Here we report, using SAuPd, the first example of Pd nanoparticle-catalyzed, unactivated C(sp^3)–H bond functionalization of amides, using 8-aminoquinoline as a directing group, to yield ethynylated products. The low leaching properties of SAuPd enabled it to be recycled and reused 10 times for C(sp^3)–H bond functionalization.

Keywords: alkynylation; C–H bond functionalization; nanoparticles; palladium; recyclable catalysts

Transition metal-catalyzed C–C bond formations *via* C–H bond activation have been the subject of many investigations in recent years.[1] In recent decades, direct C(sp^2)–H activation of (hetero)arenes and olefins has been extensively studied, and has found important applications in organic synthesis.[2] In comparison, much less research has been devoted to the activation of the more "inert" C(sp^3)–H bonds of alkyl groups; C(sp^3)–H bond functionalization is much more difficult because of the absence of assistance by π-orbitals, which efficiently interact with transition metal centers.[3] Among various pathways successfully used under homogeneous conditions to achieve such functionalization, Pd-catalyzed C(sp^3)–H activation has advantages and potential applications because of its good reactivity and controllable selectivity compared with other transition metal-catalyzed C(sp^3)–H activations.[4]

The use of immobilized catalysts such as supported Pd nanoparticles (NPs) is a significant development in C–H activation because the catalysts can be recovered and reused several times. There are reports of Pd NP-catalyzed C(sp^2)–H activation in the literature;[5] however, the use of Pd NPs in C(sp^3)–H activation has not yet been explored.



(1)

Recently, we reported the Pd-catalyzed direct ethynylation of C(sp^3) atoms positioned β to the amide carbonyl bonds in aliphatic carboxylic acid derivatives under homogeneous conditions [Eq. (1)].[6]

In the present study, our target was to accomplish the same C(sp^3)–H activation for the same conversion using Pd NPs instead of Pd(OAc)$_2$. We used a sulfur-modified Au-supported Pd material, SAuPd, recently developed by us and prepared by piranha treated Au and Pd(OAc)$_2$ in xylene.[7a] SAuPd is an immobilized

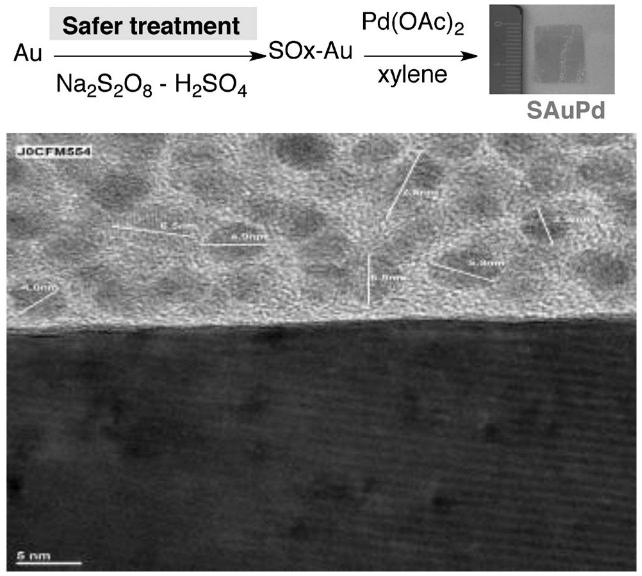


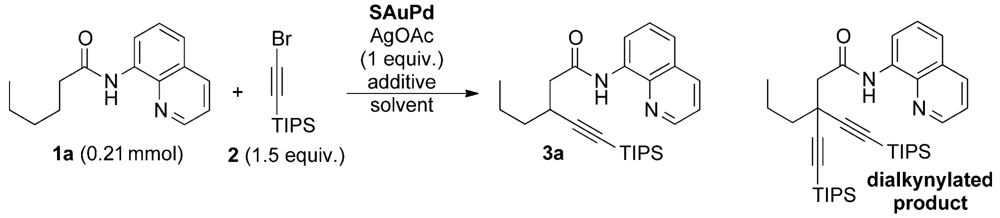
Figure 1. Preparation of SAuPd and transmission electron microscopy, TEM, image of SAuPd.

Pd catalyst with Pd NPs of size ~5 nm on the surface (Figure 1). SAuPd can repeatedly catalyze ligand-free Suzuki–Miyaura coupling and ligand-free Buchwald–Hartwig reactions; the amount of leached Pd in the reaction mixture is less than 1 ppm.[7]

Here, we report the first example of Pd NP-catalyzed unactivated C(sp^3)–H bond functionalization of amides, using SAuPd, to yield alkynylated products by simply attaching 8-aminoquinoline as a directing group. The SAuPd was reused for 10 reaction cycles, with good yields calculated based on recovered amides.

To achieve Pd NP-catalyzed unactivated C(sp^3)–H bond functionalization, we first examined the reaction of aliphatic amide **1a** and bromoalkyne **2** (Table 1). When the reaction was performed under the conditions of conventional system using SAuPd[8] instead of $Pd(OAc)_2$,[6] after 66 h the desired ethynylated product **3a** was obtained in 41% isolated yield along with 53% of unreacted **1a** (entry 1). Next, to determine the appropriate reaction conditions, solvent screening was performed. With EtOH, dichloroethane, or mesitylene as the solvent, only a trace of product **3a** was isolated, and the reaction did not proceed at all with dimethylformamide (data not shown). We then performed the reaction in xylene at 135 °C for 72 h, giving **3a** in 44% isolated yield; the dialkynylated product was generated in 11% isolated yield and 40% of **1a** was recovered (entry 2). We found that when the amount of xylene was increased, the isolated yield of product **3a** increased slightly, until the solvent volume reached 2 mL (entries 3 and 4). When 3 mL of xylene were used, the isolated yield of **3a** decreased (entry 5). At high temperature (135 °C, entries 2–5) the corresponding dialkynylated product was obtained as a by-product. To minimize dialkynylated product formation, we performed the reaction

Table 1. Effects of solvent, solvent amount, and temperature.

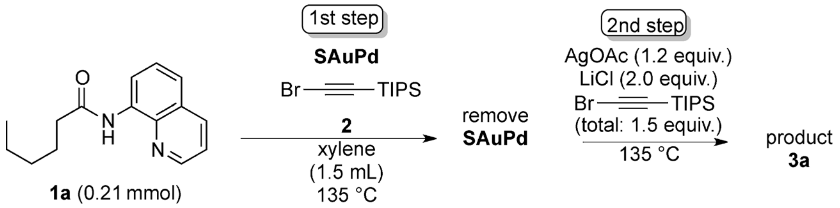


Entry	Solvent (mL)	Additive (equiv.)	Temp. [°C][a]	Time [h]	Yield [%][b]		
					3a	Dialkynylated product	**1a**
1	toluene (1.0)	LiCl (1.0)	110	66	41	–	53
2	xylene (1.0)	LiCl (1.0)	135	72	44 (89)	11	40
3	xylene (1.5)	LiCl (1.0)	135	24	51 (71)	12	32
4	xylene (2.0)	LiCl (1.0)	135	24	52	24	14
5	xylene (3.0)	LiCl (1.0)	135	24	44	16	35
6	xylene (2.0)	LiCl (1.0)	120	44	28	–	58
7	xylene (2.0)	LiCl (1.0)	110	41	20	–	60
8	xylene (1.5)	LiCl (2.0)	135	24	51 (90)		43
9	xylene (1.5)	LiCl (3.0)	135	24	40 (91)		55
10	xylene (1.5)	*N*-acetyl-L-leucine (0.3)	110	48	25 (90)	–	70
11	xylene (1.5)	*N*-acetyl-L-leucine (0.3)	135	24	52 (78)	11	35
12	xylene (1.5)	pivalic acid (1.0); LiCl (1.0)	135	24	26 (91)	–	68
13	xylene (1.5)	CsOPiv (0.3); Cs_2CO_3 (0.3)	135	44	47 (91)	–	41

[a] Bath temperature.

[b] Isolated yields, and yields calculated based on recovered amides **1a** in parentheses.

Table 2. Recycling of SAuPd from first to 10th cycles.



Entry	Conditions			Yield of **3a** [%][a]									
	2 (equiv.)	Reaction time [h]		1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th
		1st step	2nd step										
1	0.75	6	18	53 (89)									
2	0.75	6	10	52 (89)	53 (91)	42 (82)	23 (70)						
3	0.75	4	10	39 (89)	31 (84)								
4	0.75	5	10	52 (88)	52 (88)	52 (88)	48 (86)	30 (88)	17 (86)				
5	0.90	4	10	53 (91)	52 (89)	52 (87)	51 (92)	50 (91)	42 (85)	37 (78)	33 (83)	25 (86)	16 (84)

[a] Isolated yields, and yields calculated based on recovered amides **1a** in parentheses.

at lower temperatures, but the isolated yield of **3a** gradually decreased (entries 6 and 7). The isolated yields and yields calculated based on recovered amides for product **3a** were excellent when we used xylene (1.5 mL) as the solvent at 135 °C (entry 3).

From Table 1, entries 1–5, it can be seen that at 135 °C the isolated yield of the expected product **3a** was higher, but a dialkynylated product was formed. To reduce dialkynylated product generation, we performed the reaction in the presence of other additives (Table 1, entries 8–13). When 1 equiv. of LiCl was used, the isolated yield of dialkynylated product was 12% (entry 3); however, the dialkynylated product was not formed in the presence of 2.0 equiv. of LiCl (entry 8). In the case of 3.0 equiv. of LiCl, the dialkynylated product was not produced, but the isolated yield of **3a** decreased (entry 9). We then used an *N*-protected amino acid instead of LiCl because *N*-protected amino acids[9] are known to promote activation of various C(sp^3)−H bonds. At 110 °C, the yield of **3a** was lower and no dialkynylated product was produced (entry 10); the isolated yield of **3a** increased at higher temperature, but 11% of dialkynylated product was produced (entry 11). With pivalic acid[10] or CsOPiv, **3a** was obtained in 26% and 47% isolated yields, together with 68% and 41% of recovered **1a**, respectively (entries 12 and 13). We also used various oxidants such as TPAP, TEMPO, and iodobenzene diacetate instead of AgOAc, but none of them gave better results (data not shown). We concluded that the reaction conditions of entry 8 avoided generation of a dialkynylated product; **3a** was isolated in good isolated yield and yields of product **3a** calculated based on recovered amides were excellent.

In the presence of AgOAc as the oxidant, SAuPd released too much Pd in the reaction mixture, therefore to control Pd leaching from SAuPd to the amount needed for catalyzing C(sp^3)−H activation, we divided the reaction conditions into two steps.[11] The first step was Pd leaching from SAuPd in contact with amide **1a** and bromoalkyne **2**; the second step was C(sp^3)−H activation and ethynylation (Table 2). After the first step, we removed the SAuPd from the system, and it was washed and used for subsequent cycles. Amide **1a** (0.206 mmol), bromoalkyne **2** (0.75 equiv.), and SAuPd in xylene (1.5 mL) were heated at 135 °C for 6 h and then SAuPd was removed. AgOAc (1.2 equiv.), LiCl (2.0 equiv.), and bromoalkyne **2** (0.75 equiv.) were then added to the reaction mixture, and the mixture was stirred for 18 h to give **3a** in 53% isolated yield (entry 1). We found that the reaction in the second step finished within 10 h, but the isolated yield of **3a** decreased, after the third cycle (entry 2). When the other conditions were kept the same but the reaction mixture in the first step was heated for 4 h and 5 h, **3a** was obtained in 39% and 52% isolated yields, respectively (entries 3 and 4). In entry 4, heating for 5 h caused too much Pd leaching from SAuPd in cycles one to three, which is why the isolated yields of **3a** decreased after the 4th cycle. Finally, we optimized the conditions. When a solution of **2** (0.90 equiv.), amide **1a** (0.206 mmol), and SAuPd was heated at 135 °C for 4 h in the first step, and the conditions in the second step remained the same, we successfully recycled SAuPd 10 times, although the isolated yields gradually decreased after the fifth cycle (entry 5). We obtained moderate to low isolated yields of the desired alkynylated products, but yields calculated based on recovered amides in 10th repeated use were almost the same as those under homogeneous conditions.[6]

We measured the amount of immobilized Pd in SAuPd and the leached Pd in the reaction mixture, using inductively coupled plasma mass spectroscopy

Table 3. Amount of Pd in reaction mixture of **1a** and **2**,[a] and in SAuPd.

	Amount of leached Pd (ng) in reaction mixture[b,c,d] and HPLC yield of **3a**[e]											Immobilized Pd on SAuPd (μg)[c]	
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	Total	before use	after use
leached Pd (ppm, mmol%)	1710±327 (10, 8)	1203±510 (7, 5)	906±622 (5, 4)	570±217 (3, 3)	743±448 (4, 3)	570±216 (3, 3)	303±118 (2, 2)	480±108 (3, 3)	323±115 (2, 2)	233±110 (1, 1)	7041±2791	78±41	7±4
isolated yield[e]	53 (90)	51 (89)	50 (89)	49 (88)	46 (88)	40 (86)	36 (86)	31 (87)	23 (86)	14 (85)			

[a] *Reaction conditions:* **1a** (0.206 mmol), **2** (1.5 equiv.), AgOAc (1.2 equiv.), LiCl (2.0 equiv.) xylene (1.5 mL), 135 °C, 14 h.
[b] The entire reaction mixture was acidified and subjected directly to ICP-MS.
[c] The standard deviation was calculated from three sets of samples.
[d] Numbers in parentheses indicate amount of leached Pd in ppm and the loading of Pd catalyst (mmol%) used in these reactions, respectively.
[e] Data in this row indicate average HPLC yield of **3a** from three sets of reactions and average yields calculated based on recovered amides **1a** in parentheses.

(ICP-MS) to know the real loading of Pd catalyst used in these reactions. The amounts of Pd in SAuPd were determined before and after the 10th reaction cycle, under the optimized conditions. Table 3 shows that the amounts of immobilized Pd in SAuPd before and after the reactions were 78 ± 41 μg and 7 ± 4 μg, respectively. The amount of Pd released after cooling in each cycle was low; the turnover numbers (TONs) for C(sp^3)−H activation were high [233–1710 ng (1–10 ppm) for 0.206 mmol scale reaction; TON = 6790–26,045, which were calculated based on the amount of leached Pd in the reaction mixture and isolated yield of **3a**].

To generalize the SAuPd -catalyzed direct ethynylation *via* C(sp^3)−H bonds functionalization, we examined the SAuPd catalytic activities of the reactions for 10 cycles, using amides **1b–1i** (Table 4). We used the strategy used for Table 2, entry 5 for SAuPd recycling. All substrates shown in Table 2 gave β-functionalized products. Substrates with sterically demanding cyclohexyl and phenyl groups, **1b** and **1c**, were used successfully for 10 cycles (entries 1 and 2). The alkynylations also tolerated a wide range of functional groups such as ethers **1d** and **1h** (entries 3 and 7), esters **1e** (entry 4), and halides **1f** (entry 5). The C(sp^3)−H bonds adjacent to the benzylic position (**1g** and **1h**) similarly underwent alkylation without reoptimization of the catalytic system (entries 6 and 7). The γ-aminobutyric acid derivative **1i** also gave the alkynylated product, and the *N*-Boc and *N*-benzyl protecting groups were intact (entry 8).[12]

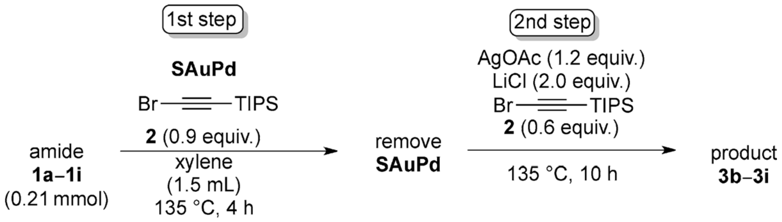
In summary, we developed a new strategy for Pd-NP-catalyzed direct ethynylation of aliphatic carboxylic acid derivatives *via* C(sp^3)−H bond functionalization at the β positions of amides, with 8-aminoquinoline as a directing group. We obtained moderate yields of the desired alkynylated products, but yields calculated based on recovered amides were almost the same as those obtained under homogeneous conditions. Because of the low leaching properties of SAuPd, the catalyst could be recycled more than 10 times. This protocol shows that Pd NPs are effective catalysts for C(sp^3)−H bond activation.

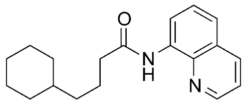
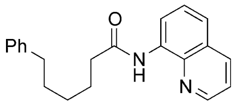
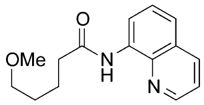
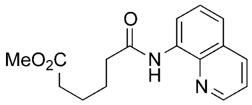
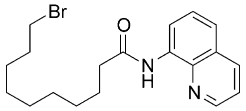
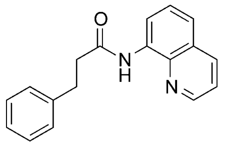
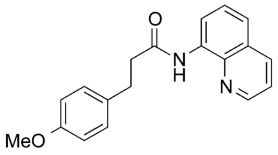
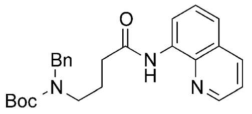
Experimental Section

Preparation of *S*ulfur-Modified *A*u Supported *Pd* Material, SAuPd

To stirring ice-cooled 98% H_2SO_4 (4.7 g) was added $Na_2S_2O_8$ (4.0 g) in a small portions and then crushed ice (13.0 g) and water (4.0 g) were added to the above solution while the temperature was kept below 15 °C. When all the salt had dissolved to a homogeneous solution, the Au (100 mesh, 14×12 mm^2, 100.7 mg) was placed in the above solution (3.0 mL) for 5 min and then washed first by H_2O (3.0 mL × 10) and then with EtOH (3.0 mL × 6). The resulted Au mesh

Table 4. Direct ethynylation of amides **1b–1i** using SAuPd, *via* C(sp^3)–H bond functionalization.



Entry	Amide		Yield of **3** [%][a]									
			1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th
1		**1b**	63 (86)	63 (84)	62 (84)	59 (84)	53 (83)	40 (82)	37 (84)	32 (83)	30 (80)	21 (79)
2		**1c**	43 (81)	42 (80)	42 (80)	41 (80)	39 (79)	32 (80)	27 (78)	22 (78)	16 (76)	12 (76)
3		**1d**	41 (81)	39 (82)	40 (81)	37 (82)	32 (82)	25 (80)	22 (80)	16 (78)	13 (78)	10 (77)
4		**1e**	45 (84)	44 (84)	41 (83)	42 (83)	38 (82)	32 (81)	26 (79)	22 (79)	17 (80)	15 (79)
5		**1f**	38 (84)	39 (85)	38 (84)	35 (84)	34 (83)	30 (81)	24 (78)	20 (80)	14 (80)	10 (80)
6		**1g**	45 (91)	46 (89)	45 (88)	45 (88)	38 (86)	35 (80)	31 (78)	24 (76)	20 (76)	18 (77)
7		**1h**	31 (74)	30 (74)	31 (73)	30 (73)	29 (72)	26 (71)	21 (70)	18 (70)	15 (70)	10 (69)
8		**1i**	31 (75)	30 (74)	26 (73)	29 (72)	27 (70)	22 (71)	19 (71)	16 (70)	12 (71)	9 (71)

[a] Isolated yields, and yields calculated based on recovered amides **1** in parentheses.

was placed in a round-bottom flask and dried for 10 min under reduced pressure (*ca.* 6 mmHg). The resulting sulfur-modified Au was placed in a solution of Pd(OAc)$_2$ (5.3 mg, 0.023 mmol) in xylene (3.0 mL) and stirred at 100 °C for 12 h under an argon atmosphere. Then it was rinsed with xylene (3.0 mL × 50) and, after vacuum drying, it was placed in xylene (3.0 mL) and heated at 135 °C for 12 h. Finally, it was rinsed with xylene (3.0 mL × 50) and dried under vacuum for 10 min to give *s*ulfur-modified *Au* supported *Pd* material SAuPd (yield: 100.8 mg, immobilized Pd: 78 ± 41 μg) and only this SAuPd was used throughout this research.

Experimental Procedure for the SAuPd-Catalyzed Alkynylation: SAuPd-Catalyzed Reaction of amide 1a with 2 (Table 2, entry 2)

To an oven-dried test tube, *N*-(8-quinolinyl)hexanamide **1a** (50.0 mg, 0.21 mmol), (bromoethynyl)triisopropylsilane **2** (80.7 mg, 0.31 mmol), AgOAc (41.3 mg, 0.25 mmol), LiCl (17.5 mg, 0.41 mmol), SAuPd and xylene (1.5 mL) were added under a gentle stream of argon. The mixture was heated for 24 h at 135 °C followed by cooling, SAuPd was removed from the reaction mixture [the SAuPd was washed with xylene (6 × 3.0 mL)]. The resulting reaction mixture was filtered through a Celite pad and concentrated under vacuum. The residue was subjected to column chromatography on silica gel (eluent: hexane/$Et_2O = 80\%$ to 75%) to afford the desired alkynylated product **3a** as a colorless oil; yield: 44.7 mg [51% (90%)].

Typical Experimental Procedure for the SAuPd-Catalyzed Alkynylation: SAuPd-Catalyzed Reaction of Amide 1a with 2 (Table 3, entry 8)

To an oven-dried test tube, *N*-(8-quinolinyl)hexanamide **1a** (50.0 mg, 0.21 mmol), (bromoethynyl)triisopropylsilane **2** (50.0 mg, 0.19 mmol), SAuPd and xylene (1.5 mL) were added under a gentle stream of argon. The mixture was heated for 4 h at 135 °C followed by cooling, SAuPd was removed from the reaction mixture [the SAuPd was washed with xylene (6 × 3.0 mL) and kept for next cycle]. The (bromoethynyl)triisopropylsilane **2** (30.6 mg, 0.18 mmol), AgOAc (41.3 mg, 0.25 mmol) and LiCl (17.5 mg, 0.41 mmol) were added into the above reaction mixture under a gentle stream of argon. The mixture was stirred for 10 h at 135 °C and followed by cooling, the mixture was filtered through a Celite pad and concentrated under vacuum. The residue was subjected to column chromatography on silica gel (eluent: hexane/$Et_2O = 80\%$ to 75%) to afford the desired alkynylated product **3a** as a colorless oil; yield: 46.6 mg [53% (91%)]. The above reaction process was maintained as for 2nd cycle and this procedure was repeated for a total 10 cycles.

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References

[1] Reviews a) G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726–11743; b) R. I. McDonald, G. Liu, S. S. Stahl, *Chem. Rev.* **2011**, *111*, 2981–3019; c) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169; d) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624–655; e) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196–5217; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115; f) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242–3272; g) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976–10011; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826; h) O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074–1086; i) F. Collet, R. H. Dodd, P. Dauban, *Chem. Commun.* **2009**, 5061–5074; j) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335–344; k) A. A. O. Sarhan, C. Bolm, *Chem. Soc. Rev.* **2009**, *38*, 2730–2744; l) J. C. Lewis, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2008**, *41*, 1013–1025; m) S. S. Stahl, *Angew. Chem.* **2004**, *116*, 3480–3501; *Angew. Chem. Int. Ed.* **2004**, *43*, 3400–3420; n) G. Dyker, *Angew. Chem.* **1999**, *111*, 1808–1822; *Angew. Chem. Int. Ed.* **1999**, *38*, 1698–1712.

[2] For selected examples of functionalization of aromatic C–H bonds, see a) E. J. Hennessy, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 12084–12085; b) F. Faccini, E. Motti, M. Catellani, *J. Am. Chem. Soc.* **2004**, *126*, 78–79; c) N. P. Grimster, C. Gauntlett, C. R. A. Godfrey, M. J. Gaunt, *Angew. Chem.* **2005**, *117*, 3185–3189; *Angew. Chem. Int. Ed.* **2005**, *44*, 3125–3129; d) L.-C. Campeau, S. Rousseaux, K. Fagnou, *J. Am. Chem. Soc.* **2005**, *127*, 18020–18021; e) H. A. Chiong, Q.-N. Pham, O. Daugulis, *J. Am. Chem. Soc.* **2007**, *129*, 9879–9884; f) K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2007**, *129*, 11904–11905; g) D.-H. Wang, T.-S. Mei, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 17676–17677; h) B.-J. Li, S.-L. Tian, Z. Fang, Z.-J. Shi, *Angew. Chem.* **2008**, *120*, 1131; *Angew. Chem. Int. Ed.* **2008**, *47*, 1115; i) X. Zhao, Z. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 8136–8137; j) S. H. Cho, S. J. Hwang, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 9254–9256.

[3] Reviews a) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654–2672; b) O. Daugulis, H. Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074–1086; c) O. Baudoin, *Chem. Soc. Rev.* **2011**, *40*, 4902–4911.

[4] Recent examples of Pd-catalyzed C(sp^3)–H bond activation a) J. He, M. Wasa, K. S. L. Chan, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 3387–3390; b) M. Figg, M. Wasa, J.-Q. Yu, D. G. Musaev, *J. Am. Chem. Soc.* **2013**, *135*, 14206–14214; c) E. T. Nadres, G. I. F. Santos, D. Shabashov, O. Daugulis, *J. Org. Chem.* **2013**, *78*, 9689–9714; d) S. Zhang, G. He, W. A. Nack, Y. Zhao, Q. Li, G. Chen, *J. Am. Chem. Soc.* 2013, 135, 2124–2127; e) K. J. Stowers, A. Kubota, M. S. Sanford, *Chem. Sci.* **2012**, *3*, 3192–3195; f) S. Aspin, A.-S. Goutierre, P. Larini, R. Jazzar, O. Baudoin, *Angew. Chem.* **2012**, *124*, 10966–10969; *Angew. Chem. Int. Ed.* **2012**, *51*, 10808–10811; g) W. R. Gutekunst, R. Gianatassio, P. S. Baran, *Angew. Chem.* **2012**, *124*, 7625–7628; *Angew. Chem. Int. Ed.* **2012**, *51*, 7507–7510.

[5] L. L. Chng, J. Zhang, J. Yang, M. Amoura, J. Y. Ying, *Adv. Synth. Catal.* **2011**, *353*, 2988–2998.

[6] Y. Ano, M. Tobisu, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 12984–12986.

[7] a) N. Hoshiya, M. Shimoda, H. Yoshikawa, Y. Yamashita, S. Shuto, M. Arisawa, *J. Am. Chem. Soc.* **2010**, *132*, 7270–7272; b) N. Hoshiya, S. Shuto, M. Arisawa, *Adv. Synth. Catal.* **2011**, *353*, 743–748; c) M. Al-Amin, T. Honma, N. Hoshiya, S. Shuto, M. Arisawa, *Adv. Synth. Catal.* **2012**, *354*, 1061–1068; d) M. Al-Amin, S. Arai, N. Hoshiya, T. Honma, Y. Tamenori, T. Sato, M. Yokoyama, A. Ishii, M. Takeuchi, T. Maruko, S. Shuto, M. Arisawa, *J. Org. Chem.* **2013**, *78*, 7575–7581; e) M. Al-Amin, M. Akimoto, T. Tameno, Y. Ohki, N. Takahashi, N. Hoshiya, S. Shuto, M. Arisawa, *Green Chem.* **2013**, *15*, 1142–1145.

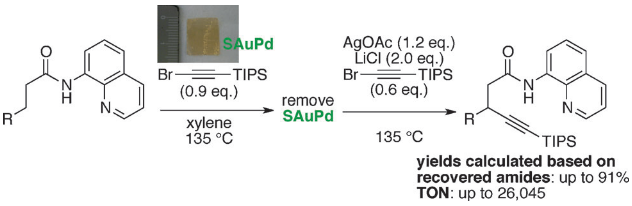
[8] In these experiments, we used 1.2 cm × 1.4 cm, 100 mesh, SAuPd, which contained 50–100 μg of Pd.

[9] B.-F. Shi, N. Maugel, Y.-H. Zhang, J.-Q. Yu, *Angew. Chem.* **2008**, *120*, 4960–4964; *Angew. Chem. Int. Ed.* **2008**, *47*, 4882–4886.

[10] S. Rousseaux, S. I. Gorelsky, B. K. W. Chung, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 10692–10705.

[11] SAuPd releases active Pd species through oxidative addition with halides.[7b,c] In Suzuki–Miyaura coupling and/or Buchwald–Hartwig reactions, which are catalyzed by Pd(0), active Pd species return to the SAuPd surface. However, in this C(sp^3)–H activation, which requires AgOAc, the active species is Pd(II) and has difficulty returning to the SAuPd surface. To achieve SAuPd recyclability, it was necessary to leach the minimum amount of Pd species from SAuPd to the reaction mixture, to keep sufficient Pd in the SAuPd for the next cycle.

[12] In this research we used only (bromoethynyl)triisopropylsilane **2** as an alkynyl bromide.


SAuPd
Br—≡—TIPS
(0.9 eq.)
xylene
135 °C
remove
SAuPd
AgOAc (1.2 eq.)
LiCl (2.0 eq.)
Br—≡—TIPS
(0.6 eq.)
135 °C
O
N
H
N
R
TIPS
yields calculated based on recovered amides: up to 91%
TON: up to 26,045