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Palladium-Catalyzed Catellani *ortho*-Acylation Reaction: An Efficient and Regiospecific Synthesis of Diaryl Ketones

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Abstract: *A palladium-catalyzed, norbornene-mediated Catellani ortho-acylation reaction was developed by the use of either acyl chlorides or acid anhydrides as acylation reagents. The addition of more than a stoichiometric amount of H_2O is crucial for this transformation when acid chlorides are used, and kinetic studies indicate that the active acylation reagent is possibly an acid anhydride.*

Diaryl ketones are important building blocks or intermediates in the synthesis of pharmacological compounds and even complex natural products,[1] and they represent an important class of subunits in natural products and drugs or drug candidates, such as OXi8008,[2] Amiodarone hydrochloride, Rubialatins B,[3] and Acredinone B (Figure 1).[4] The most

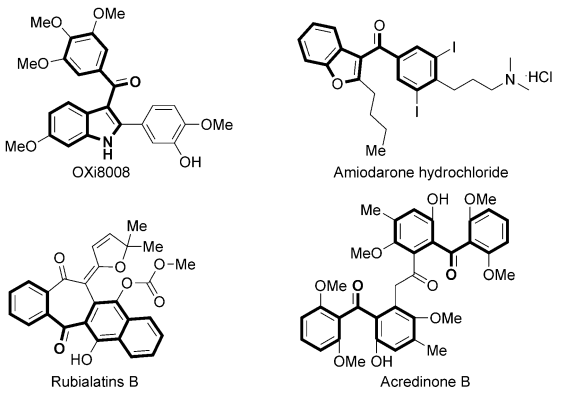
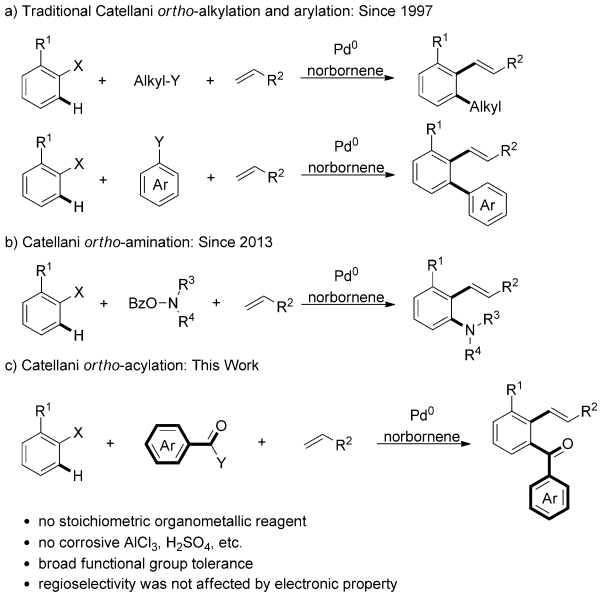


Figure 1. Representative drug or drug candidates and natural products which contain diaryl ketones.

general method for the preparation of these diaryl ketone compounds is Friedel–Crafts acylation. However, this protocol suffers from harsh reaction conditions and low regioselectivity, and sometimes the formation of the undesired regioisomers. Alternatively, by the use of organometallic reagents, a series of diaryl ketones can be accessed with or without the transition-metal catalysts.[1,5,6] However, the limitations of these strategies are the requirement of stoichiometric amounts of organometallic reagents and the limited substrate scope. Thus the development of new, practical, and highly functional-group tolerant methods for the synthesis of diaryl ketones is still desirable.

During the synthesis of natural products containing polysubstituted arenes, we realized that the Catellani reaction, which was developed by Catellani in 1990s,[7] is a powerful tool for the construction of multisubstituted arenes. Since the development of the reaction, only aliphatic chains and aryl groups could be introduced to the position *ortho* to the halogen atom (Scheme 1 a).[8,9] During this period, studies



Scheme 1. Palladium-catalyzed Catellani reaction of aryl halides.

from the groups of Lautens, Catellani, and others mostly focused on the development of versatile termination reagents, including inter- or intramolecular alkenes, organo boronic acids, cyano anion, amines, electron-rich arenes, alkynes, carbenes, etc., and quite a number of structurally diverse arenes were synthesized. Very recently, progress in this area was made by the groups of Dong and later by Chen, who developed an *ortho* amination protocol for the synthesis of aniline analogues by the use of *O*-benzylhydroxylamines as amination reagents (Scheme 1 b).[10]

Given these developments and our interest in natural products synthesis, we reasoned that by using either acyl chlorides or acid anhydrides acyl groups might be chemoselectively introduced at the position *ortho* to the halogen (Scheme 1 c). As a result, other functionalities, such as alkenes and alcohols, as well as esters (by Baeyer–Villiger oxidation)[11] could be easily accessed from the ketones. The

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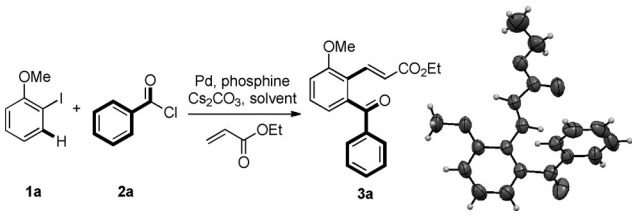
advantages of this strategy are: 1) the reaction proceeds with broad substrate scope since neither organometallic reagents nor strong Lewis or Brønsted acids are needed; 2) the reaction provides regiospecific products and the selectivity is not affected by the electronic properties of aryl halide compounds.

Our initial trial commenced with the reaction of 2-iodoanisole (**1a**) with benzoyl chloride (**2a**) in the presence of palladium chloride and tri(2-furyl)phosphine (TFP). To our disappointment, with fresh distilled benzoyl chloride in dry 1,4-dioxane the reaction did not take place under an inert atmosphere (Table 1, entry 1). However, it was interesting to

Table 1: Optimization of reaction conditions.[a]



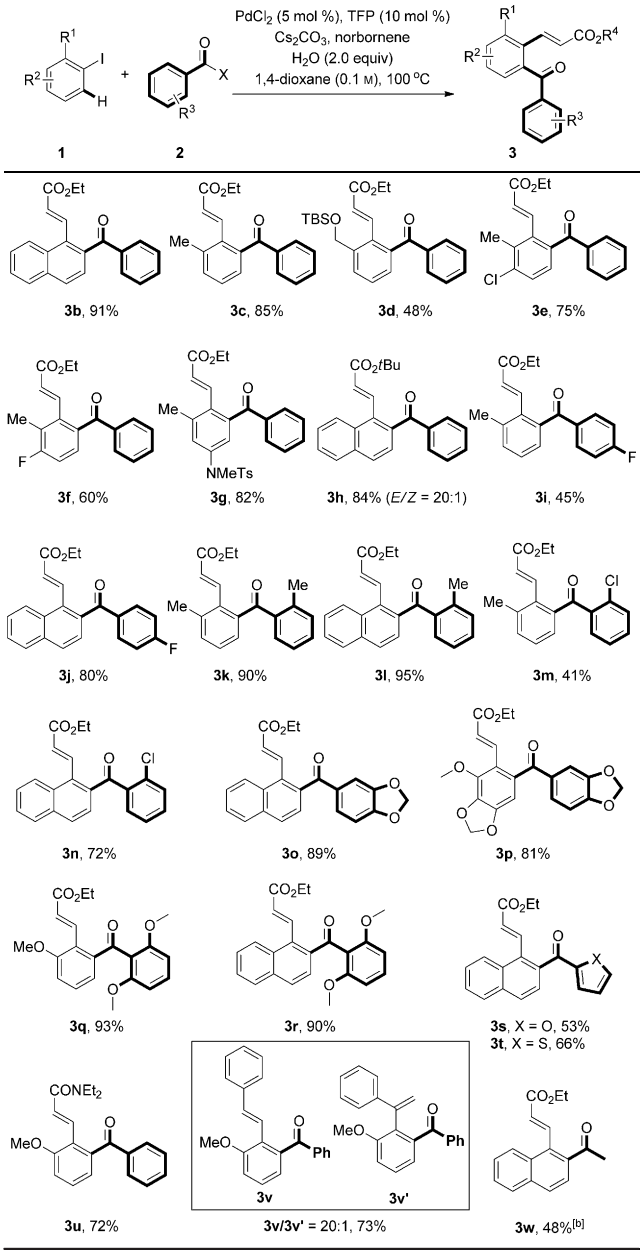
Entry	Palladium	Solvent	H_2O (equiv)	Yield [%][b]
1	$PdCl_2$	1,4-dioxane	–	trace
2[c]	$PdCl_2$	1,4-dioxane	1.0	65
3[c]	$PdCl_2$	1,4-dioxane	2.0	81
4	$PdCl_2$	1,4-dioxane	2.5	59
5	$PdCl_2$	1,4-dioxane	3.0	60
6	$PdCl_2$	PhMe	2.0	34
7	$PdCl_2$	CH_3CN	2.0	50
8	$[Pd_2(dba)_3]$	1,4-dioxane	2.0	23
9[d]	$[Pd(PPh_3)_2Cl_2]$	1,4-dioxane	2.0	35

[a] The reaction was conducted with **1a** (0.20 mmol), **2a** (3.0 equiv), Pd (5 mol%), TFP (10 mol%), and Cs_2CO_3 (3.0 equiv) at 100°C for 10 h. [b] Yield of isolated product. [c] For the relative reaction rates, see Figure 2. [d] No TFP was added. dba = dibenzylideneacetone.

observe that a small amount of the acylated product **3a** could be detected after the reaction was exposed to air for a very short time during TLC analysis. After very careful optimization, it was found that the addition of 2.0 equivalents of H_2O gave a good yield of **3a** and proceeded with a considerable reaction rate (entries 2 and 3). The structure of **3a** was unambiguously confirmed by single-crystal X-ray analysis.[12] An increase in the loading of H_2O to either 2.5 or 3.0 equivalents only had a negative effect, and the yields fell to around 60% (entries 4 and 5). The screening of other solvents, such as toluene or acetonitrile, did not lead to better results (entries 6 and 7). Further investigation revealed that $[Pd_2(dba)_3]$ and $[Pd(PPh_3)_2Cl_2]$ showed low catalytic activity for this transformation (entries 8 and 9).

With the optimum reaction conditions in hand, we explored the substrate scope of the palladium-catalyzed *ortho*-acylation reaction (Table 2). 1-Iodonaphthalene and other *ortho*-substituted iodobenzenes are good substrates, and the corresponding reactions afforded the desired acylation products in good to excellent yields (**3b–g**). However, the reaction only delivered **3d** in 48% yield, probably because of the base-sensitive the silyl group. *tert*-Butyl acrylate could

Table 2: Substrate scope.[a]

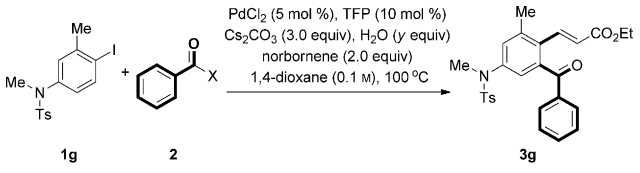


[a] The reaction was conducted with **1** (0.20 mmol), acid chloride (**2**; 3.0 equiv), acrylate (2.0 equiv), $PdCl_2$ (5 mol%), TFP (10 mol%), Cs_2CO_3 (3.0 equiv), H_2O (2.0 equiv), and norbornene (2.0 equiv) in 1,4-dioxane (0.1 M) at 100°C for 10–15 h. [b] The reaction was conducted at 110°C for 10 h. TBS = *tert*-butyldimethylsilyl, Ts = 4-toluenesulfonyl.

also be used as a termination reagent, and led to a slightly decreased product yield (**3h**). A number of functionalized benzoyl chlorides were subjected to the reaction, and decent to excellent yields were achieved (**3i–n**). Notably, piperonyloyl chloride and 2,6-dimethoxybenzoyl chloride were compatible substrates, and the respective ketone moieties exist in a number of important natural products (**3o–r**). This transformation was also applicable to heteroaromatic acid chlorides, such furan-2-carbonyl chloride and thiophene-2-carbonyl chloride, to give the corresponding ketones in moderate to good yields (**3s** and **3t**). The reaction with acrylate amide as

the termination reagent also worked uneventfully (**3u**). Styrene is a compatible alkene, and the reaction smoothly gave stilbene derivatives in moderate yield with a regioselectivity of about 20:1 (**3v** and **3v′**). Primary studies on the aliphatic acid chlorides showed that the acetyl group can also can be introduced, albeit in a lower yield (**3w**).

To gain insight into the mechanism, several control experiments were performed and the conversion was monitored by NMR spectroscopy (Figure 2). The reaction almost



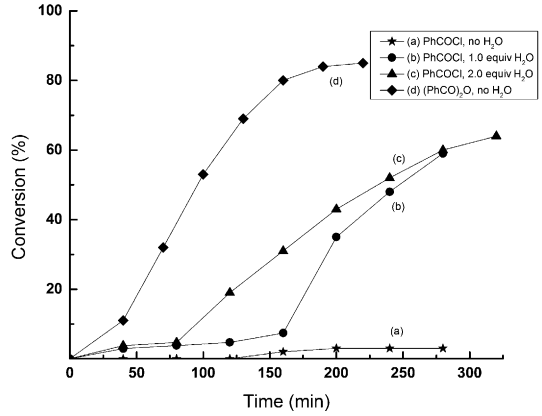
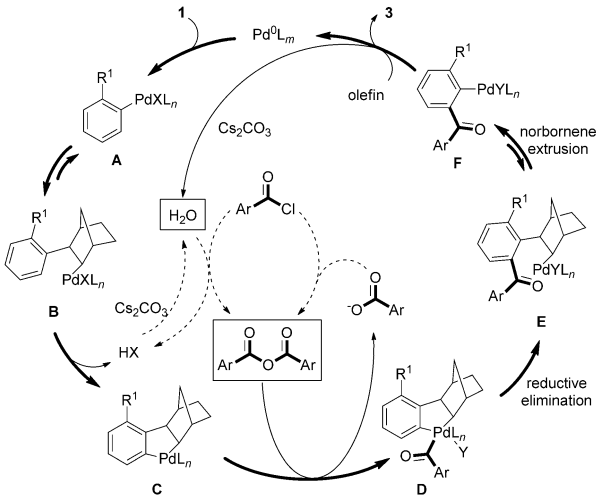


Figure 2. Kinetic studies: a) PhCOCl (3.0 equiv) was used in the absence of H_2O. b) PhCOCl (3.0 equiv) was used in the presence of 1.0 equiv of H_2O. c) PhCOCl (3.0 equiv) was used in the presence of 2.0 equiv of H_2O. d) Benzoic anhydride (2.0 equiv) was used in the absence of H_2O.

did not take place when benzoyl chloride was used in dry 1,4-dioxane under argon atmosphere. The addition of 1.0 or 2.0 equivalents of H_2O dramatically promoted the reaction. However, an induction period was observed for these reactions, and during this period the formation of an acid anhydride could be observed by NMR spectroscopy and mass spectra. Moreover, the reaction rate was much faster when an acid anhydride was used instead of an acid chloride. These results indicated that acid anhydrides could be the active acylating agents.

Based on these experimental results, a catalytic cycle is proposed (Scheme 2). Oxidative addition of palladium(0) to arylhalides and norbornene insertion, with subsequent palladation, generates the pallacycle intermediate **C**. This pallacycle undergoes oxidative addition with acid anhydride, rather than acid chloride, to form the acylpalladium intermediate **D** and generates one molecule of acid anion.[13] The carboxylic acid anion reacts with acid chloride to generate an acid anhydride. The addition of H_2O or in situ generated H_2O accelerates the formation of anhydrides. Theoretically a catalytic amount of H_2O is enough for this transformation, but a stoichiometric amount of water is required to achieve



Scheme 2. Plausible catalytic cycle.

a reasonable reaction rate. Reductive elimination of **D** then delivers the alkyl palladium **E**, which undergoes norbornene extrusion and a subsequent classic palladium-catalyzed reaction to give the products **3**.

In conclusion, we have developed an efficient Catellani *ortho*-acylation reaction by the use of either acid chlorides or anhydrides as the acylating reagents. The key step of this transformation is the oxidative addition of the pallacycle to the acid anhydride to generate an acylated palladium(IV) intermediate. The reaction demonstrates a general acylation protocol of aromatic halides with good functional-group tolerance. Furthermore, some unusual acylated compounds were synthesized, which cannot be easily accessed by traditional acylation methods. Studies on the details of the mechanism and applications in natural product syntheses are ongoing in our laboratory. Further studies will also focus on the development of more efficient transformations with either aliphatic acid chlorides or anhydrides.

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[1] a) R. K. Dieter, *Tetrahedron* **1999**, *55*, 4177; b) N. J. Lawrence, *J. Chem. Soc. Perkin Trans. 1* **1998**, 1739; c) Q.-F. Hu, B. Zhou, J.-M. Huang, X.-M. Gao, L.-D. Shu, G.-Y. Yang, C.-T. Che, *J. Nat. Prod.* **2013**, *76*, 292; d) A. Shimada, I. Takahashi, T. Kawano, Y. Kimura, *Z. Naturforsch. B* **2011**, *56*, 797.

[2] M. B. Hadimani, M. T. MacDonough, A. Ghatak, T. E. Strecker, R. Lopez, M. Sriram, B. L. Nguyen, J. J. Hall, R. J. Kessler, A. R. Shirali, L. Liu, C. M. Garner, G. R. Pettit, E. Hamel, D. J. Chaplin, R. P. Mason, M. L. Trawick, K. G. Pinney, *J. Nat. Prod.* **2013**, *76*, 1668.
[3] S.-M. Zhao, Z. Wang, G.-Z. Zeng, W.-W. Song, X.-Q. Chen, X.-N. Li, N.-H. Tan, *Org. Lett.* **2014**, *16*, 5576.
[4] H. Kim, I. Yang, S.-Y. Ryu, D. H. Won, A. G. Giri, W. Wang, H. Choi, J. Chin, D. Hahn, E. Kim, C. Han, J. Lee, S.-J. Nam, W.-K. Ho, H. Kang, *J. Nat. Prod.* **2015**, *78*, 363.
[5] C. Duplais, F. Bures, I. Sapountzis, T. J. Korn, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 2968; *Angew. Chem.* **2004**, *116*, 3028.
[6] For a most recent review, see: a) X.-F. Wu, *Chem. Eur. J.* **2015**, *21*, 12252; for some typical transition-metal-catalyzed acylation reactions, see: b) X. Jia, S. Zhang, W. Wang, F. Luo, J. Cheng, *Org. Lett.* **2009**, *11*, 3120; c) Q. Shuai, L. Yang, X. Guo, O. Basle, C.-J. Li, *J. Am. Chem. Soc.* **2010**, *132*, 12212; d) R. Giri, J. K. Lam, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 686; e) Y. Lu, D. Leow, X. Wang, K. M. Engle, J.-Q. Yu, *Chem. Sci.* **2011**, *2*, 967; f) S. D. Ramgren, N. K. Garg, *Org. Lett.* **2014**, *16*, 824; g) Z. Yin, P. Sun, *J. Org. Chem.* **2012**, *77*, 11339; h) Q. Zhang, F. Yang, Y. Wu, *Chem. Commun.* **2013**, *49*, 6837; i) C. Pi, X. Cui, X. Liu, M. Guo, H. Zhang, Y. Wu, *Org. Lett.* **2014**, *16*, 5164; j) C. W. Chan, Z. Zhou, A. S. C. Chan, W. Y. Yu, *Org. Lett.* **2010**, *12*, 3926; k) P. Mamone, G. Danoun, L. J. Gooßen, *Angew. Chem. Int. Ed.* **2013**, *52*, 6704; *Angew. Chem.* **2013**, *125*, 6836.
[7] a) M. Catellani, L. Ferioli, *Synthesis* **1996**, 769; b) M. Catellani, F. Frignani, A. Rangoni, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 119; *Angew. Chem.* **1997**, *109*, 142.
[8] a) M. Catellani, *Synlett* **2003**, 298; b) M. Catellani, E. Motti, N. Della Ca', *Acc. Chem. Res.* **2008**, *41*, 1512; c) A. Martins, B. Mariampillai, M. Lautens, *Top. Curr. Chem.* **2010**, *292*, 1; d) X. Sui, R. Zhu, Z. Gu, *Synlett* **2013**, *24*, 2023.
[9] For some recent typical reports, see: a) Z. Qureshi, W. Schlundt, M. Lautens, *Synthesis* **2015**, *47*, 2446; b) X.-C. Wang, W. Gong, L.-Z. Fang, R.-Y. Zhu, S. Li, K. M. Engle, J.-Q. Yu, *Nature* **2015**, *519*, 334; c) Z. Dong, J. Wang, G. Dong, *J. Am. Chem. Soc.* **2015**, *137*, 5887; d) H. Zhang, P. Chen, G. Liu, *Angew. Chem. Int. Ed.* **2014**, *53*, 10174; *Angew. Chem.* **2014**, *126*, 10338; e) M. Sickert, H. Weinstabl, B. Peters, X. Hou, M. Lautens, *Angew. Chem. Int. Ed.* **2014**, *53*, 5147; *Angew. Chem.* **2014**, *126*, 5247; f) P.-X. Zhou, Y.-Y. Ye, J.-W. Ma, L. Zheng, Q. Tang, Y.-F. Qiu, B. Song, Z.-H. Qiu, P.-F. Xu, Y.-M. Liang, *J. Org. Chem.* **2014**, *79*, 6627; g) V. Narbonne, P. Retailleau, G. Maestri, M. Malacria, *Org. Lett.* **2014**, *16*, 628; h) L. Jiao, T. Bach, *Angew. Chem. Int. Ed.* **2013**, *52*, 6080; *Angew. Chem.* **2013**, *125*, 6196; i) X. Sui, R. Zhu, G. Li, X. Ma, Z. Gu, *J. Am. Chem. Soc.* **2013**, *135*, 9318; j) H. Weinstabl, M. Suhartono, Z. Qureshi, M. Lautens, *Angew. Chem. Int. Ed.* **2013**, *52*, 5305; *Angew. Chem.* **2013**, *125*, 5413; k) L. Jiao, E. Herdtweck, T. Bach, *J. Am. Chem. Soc.* **2012**, *134*, 14563; l) H. Liu, M. El-Salfiti, M. Lautens, *Angew. Chem. Int. Ed.* **2012**, *51*, 9846; *Angew. Chem.* **2012**, *124*, 9984; m) H. Liu, M. Ei-Salfiti, D. I. Chai, J. Auffret, M. Lautens, *Org. Lett.* **2012**, *14*, 3648; n) L. Jiao, T. Bach, *J. Am. Chem. Soc.* **2011**, *133*, 12990; o) G. Maestri, E. Motti, N. Della Ca', M. Malacria, E. Derat, M. Catellani, *J. Am. Chem. Soc.* **2011**, *133*, 8574; p) D. I. Chai, P. Thansandote, M. Lautens, *Chem. Eur. J.* **2011**, *17*, 8175; q) M.-H. Larraufie, G. Maestri, A. Beaume, E. Derat, C. Ollivier, L. Fensterbank, C. Courillon, E. Lacote, M. Catellani, M. Malacria, *Angew. Chem. Int. Ed.* **2011**, *50*, 12253; *Angew. Chem.* **2011**, *123*, 12461; r) M. Blanchot, D. A. Candito, F. Larnaud, M. Lautens, *Org. Lett.* **2011**, *13*, 1486; s) A. Martins, D. A. Candito, M. Lautens, *Org. Lett.* **2010**, *12*, 5186; t) D. A. Candito, M. Lautens, *Org. Lett.* **2010**, *12*, 3312; u) R. Ferraccioli, D. Carenzi, E. Motti, M. Catellani, *J. Am. Chem. Soc.* **2006**, *128*, 722.
[10] a) Z. Dong, G. Dong, *J. Am. Chem. Soc.* **2013**, *135*, 18350; b) Z.-Y. Chen, C.-Q. Ye, H. Zhu, X.-P. Zeng, J.-J. Yuan, *Chem. Eur. J.* **2014**, *20*, 4237; c) C. Ye, H. Zhu, Z. Chen, *J. Org. Chem.* **2014**, *79*, 8900; d) H. Shi, D. J. Babinski, T. Ritter, *J. Am. Chem. Soc.* **2015**, *137*, 3775; e) F. Sun, Z. Gu, *Org. Lett.* **2015**, *17*, 2222.
[11] G. R. Krow, *Org. React.* **1993**, *43*, 251.
[12] CCDC 1412197 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[13] A transmetallation pathway by dimetallic intermediates was also possible: a) D. J. Cárdenas, B. Martín-Matute, A. M. Echavarren, *J. Am. Chem. Soc.* **2006**, *128*, 5033; b) B. Martín-Matute, C. Mateo, D. J. Cárdenas, A. M. Echavarren, *Chem. Eur. J.* **2001**, *7*, 2341. See also Ref. [9o].

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