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Palladium(II)-Catalyzed C(sp^2)−H Carbonylation of Sterically Hindered Amines with Carbon Monoxide

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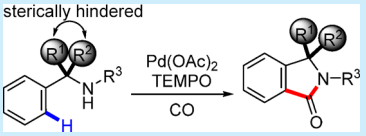
Supporting Information

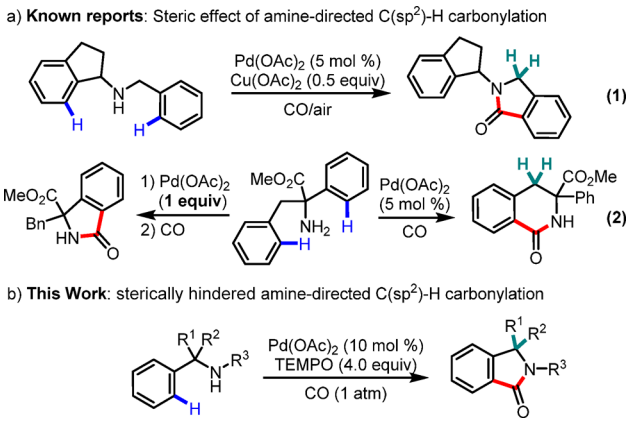
ABSTRACT: A palladium-catalyzed, amine-directed C(sp^2)−H carbonylation of α,α-disubstituted benzylamine under 1 atm of CO for the facile synthesis of sterically hindered benzolactam has been developed. The key to success is the use of 2,2,6,6-tetramethyl-1-piperidinyloxy as the crucial sole oxidant. The synthetic utility of this transformation has been demonstrated by the first concise synthesis of the natural product spiropachysin-20-one.



As the most essential and easily available C1 feedstock, the use of carbon monoxide (CO) as a carbonylation reagent has long caused extensive concern from both academia and industry.[1] Along with the rapid development of C−H activation reactions in the past decade, transition-metal-catalyzed direct insertion of carbon monoxide into inert C−H bonds has emerged as a powerful strategy to introduce a transformable carbonyl group into organic molecules.[2] Since the pioneering work of Fujiwara's group in 1980,[3] palladium-catalyzed C(sp^2)−H carbonylation with CO has been developed as a facile approach for direct C−H functionalization[4] and been used as a potential disconnecting tactic for the total synthesis of complex biologically active molecules. For example, amine-directed C−H activation/CO insertion has been used as an efficient approach to construct (benzo)-lactams, which widely exist in a variety of natural products as key skeletons.

The first example of Pd-catalyzed, amine-directed *ortho*-selective C(sp^2)−H carbonylation of benzylic amines with CO was reported by Orito and co-workers in 2004.[5] However, this reaction occurred only for α,α-unsubstituted benzylamines, rather than the sterically constrained α-substituted benzylamines (Scheme 1, eq 1).[6] Meanwhile, the Granell and Garcia group reported that while the stoichiometric palladium-mediated carbonylation of quaternary α-amino α-benzyl ester with CO gave five-membered benzolactam, the catalytic reaction furnished only six-membered isoquinolin-1-one (Scheme 1, eq 2).[7] These results clearly indicate that the steric circumstance around the C−H bond of arene was the pivotal factor of the benzylamines' reactivity. In 2011, Gaunt and co-workers described a Pd(II)-catalyzed C−H carbonylation of α-monosubstituted benzylamines with CO in 2011,[8] but more sterically hindered α,α-disubstituted amines still remained challenging in this system. It was speculated that the low reactivity of such sterically hindered amines comes from the lower coordination capacity of the nitrogen atom and higher cyclization capacity due to the steric hindrance and Thorpe−Ingold effect caused by α,α-disubstituents. To address this issue, herein, we reported a novel Pd-catalyzed C(sp^2)−H carbonylation of α,α-disubstituted benzylamines under 1 atm of CO for facile synthesis of 3,3-disubstituted isoindolin-1-ones. The key to success is the use of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as the crucial sole oxidant. The synthetic utility of this transformation has also been demonstrated by the first concise synthesis of the natural product spiropachysin-20-one.

Scheme 1. Steric Effect of Pd-Catalyzed C(sp^2)−H Carbonylation of Amines with CO



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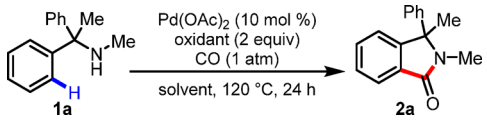
Our study commenced with examining the C(sp²)−H carbonylation with *N*-methyl-2,2-diphenylethylamine **1a** used as the pilot substrate in the presence of a catalytic amount of $Pd(OAc)_2$ (10 mol %) under 1 atm of CO in toluene at 120 °C for 24 h. Not surprisingly, only a trace amount of lactam **2a** was obtained when 0.5 equiv of $Cu(OAc)_2$ under air was used as the oxidant (entry 1, Table 1), as shown in Orito's reports.[5,6] It was speculated that the squeeze of the sterically hindered amine on the nitrogen atom causes its reduction of coordination capacity and, thus slowing the reoxidation of Pd(0) to Pd(II) catalyst might cause the agglomeration of the Pd(0) species. As a corresponding tactic to speed up the reoxidation, oxygen was used to replace air in the presence of a catalytic amount of $Cu(OAc)_2$, which afforded a slightly higher yield of **2a** (7%, entry 2, Table 1). To our delight, using stoichiometric $Cu(OAc)_2$ or O_2 directly as the sole oxidant could afford the desired product **2a** in 16% or 39% yields, respectively (entries 3 and 4, Table 1). These results clearly indicate the key role of oxidants to accelerate this transformation. As a result, a careful examination of oxidants was next carried out, which showed that most of the commonly used oxidants, such as BQ, copper salts, silver salts, $PhI(OAc)_2$, and $K_2S_2O_8$, proved to be less effective. However, to our excitement, **2a** could be furnished in almost 80% yield when TEMPO was used as the oxidant (entry 9, Table 1).[9] Unfortunately, the yield of **2a** in the reaction using toluene as the solvent afforded a poor repeatability. While decreasing the catalyst loading to 5 mol % resulted in a lower yield (entry 12, Table 1), a series of solvents have also been carefully examined. To our delight, chlorobenzene was found to be the optimal choice to give a slightly higher yield of **2a** (entry 17, Table 1). It should be noted that good repeatability has also been demonstrated for this reaction when chlorobenzene was used as the solvent instead of toluene. Notably, the benzolactam product was afforded in excellent yield in the presence of 10 mol % of $Pd(OAc)_2$ in chlorobenzene at 130 °C for 48 h (98%, entry 20, Table 1). Finally, the control experiment showed that only a trace amount of **2a** was detected without $Pd(OAc)_2$ catalyst.

With the optimized conditions in hand, we next investigated the scope of sterically hindered benzylic amines. As shown in Scheme 2, the electron-donating and -neutral groups on the phenyl ring were well tolerated in this carbonylation reaction. Not surprisingly, the subjection of electron-donating methoxy group substituted aryl amine (**1c**, **1k**, and **1l**) to the standard

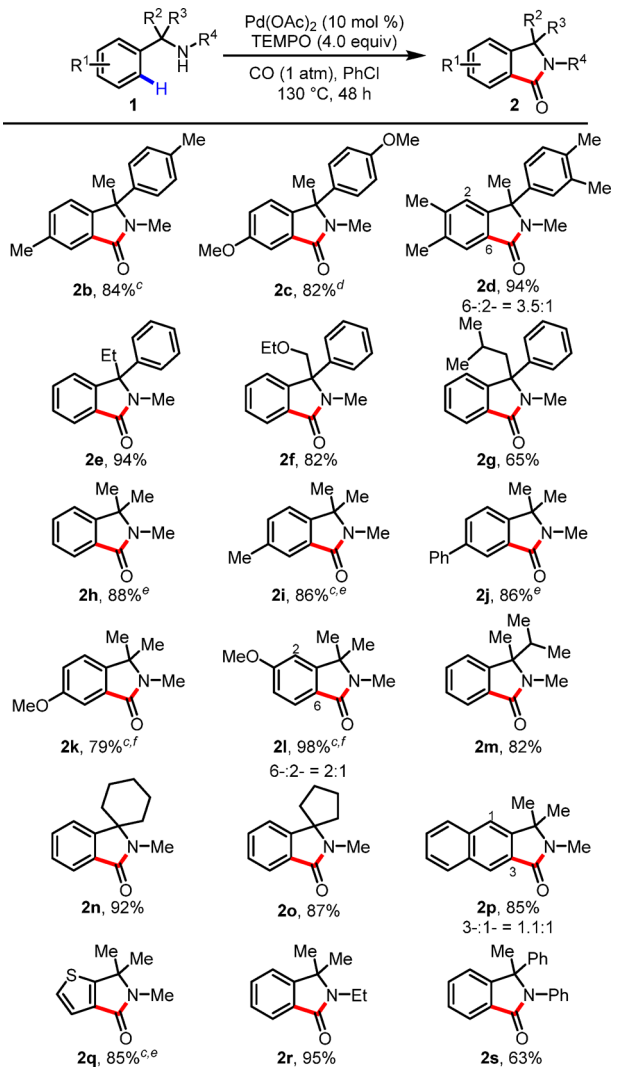
Table 1. Palladium-Catalyzed C(sp²)−H Carbonylation of Sterically Hindered Amines: Optimization of Conditions[a]



entry	oxidant (equiv)	solvent	yield[b] (%)
1	$Cu(OAc)_2$ (0.5) /air (1 atm)	toluene	trace
2	$Cu(OAc)_2$ (0.5) /O_2 (1 atm)	toluene	7
3	$Cu(OAc)_2$ (4.0)	toluene	17
4	O_2 (1 atm)	toluene	39
5	BQ (2.0)	toluene	20
6	$PhI(OAc)_2$ (2.0)	toluene	NR
7	$K_2S_2O_8$ (2.0)	toluene	trace
8	Ag_2CO_3 (2.0)	toluene	26
9	TEMPO (4.0)	toluene	76−87
10	AgOAc (4.0)	toluene	10
11	$CuCl_2$ (4.0)	toluene	26
12[c]	TEMPO (4.0)	toluene	52−76
13[c]	TEMPO (4.0)	dioxane	28
14[c]	TEMPO (4.0)	MeCN	27
15[c]	TEMPO (4.0)	DCE	trace
16[c]	TEMPO (4.0)	mesitylene	63
17[c]	TEMPO (4.0)	xylene	64
18[c]	TEMPO (4.0)	PhCl	84
19	TEMPO (4.0)	PhCl	86
20[d]	TEMPO (4.0)	PhCl	98
21[e]	TEMPO (4.0)	PhCl	trace

[a]Unless otherwise noted, the reaction conditions were as follows: **1a** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol, 10 mol %), oxidant, toluene (0.1 mol/L), CO (1 atm), 120 °C, 24 h. [b]Isolated yield. [c]$Pd(OAc)_2$ (5 mol %), 48 h. [d]130 °C, 48 h. [e]No $Pd(OAc)_2$.

Scheme 2. Palladium-Catalyzed C(sp²)−H Carbonylation of Sterically Hindered Amines: Substrate Scope[a,b]



[a]Unless otherwise noted, the reaction conditions were as follows: **1** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol, 10 mol %), TEMPO (0.8 mmol, 4.0 equiv), chlorobenzene (2 mL), CO (1 atm), 130 °C, 48 h. [b]Isolated yield. [c]120 °C. [d]$Pd(OAc)_2$ (15 mol %), 24 h. [e]$Pd(OAc)_2$ (5 mol %). [f]Toluene was used as the solvent.

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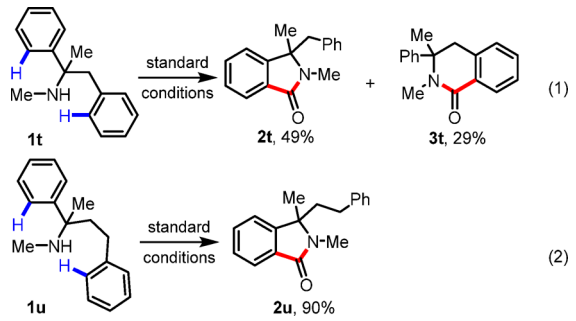
conditions furnished a relatively lower yield along with some byproducts, probably due to the decomposition of the corresponding electron-rich arenes under the oxidation conditions. To improve the yield of these electron-rich substrates, increasing the catalyst loading and reducing reaction time (**2c**) or decreasing the reaction temperature (**2k** and **2l**) has been demonstrated as effective approaches to afford good yields of the corresponding benzolactams. Moreover, meta-substituted benzylamines gave mixtures of two regioisomers, and the carbonylation occurred slightly preferentially at the less hindered C−H bond. The substituent effects on the α-position of the nitrogen atom were next examined in this transformation. To our satisfaction, a variety of α-substituents, including ethyl, ethoxymethyl, isopropyl, and isobutyl, as well as spiro-cyclohexyl and spiro-cyclopentyl, on the benzylic amines were compatible with this novel method (**2e−g**, **2m−o**). In addition, polycyclic arenes, such as naphthalene (**1p**), and heterocyclic arenes, such as thiophene (**1q**) derivatives, were also well tolerated in this reaction, with both giving the corresponding benzolactams in 85% yield. Finally, the investigation of the N-protecting groups revealed that ethyl-protected amine (**1r**) gave almost the same excellent yield as the methyl group, while the phenyl-protecting group (**1s**) reduced the yield to only moderate.

To demonstrate the different regioselectivity of our method to known reports from the groups of Orito[6] and Granell and Garcia,[7] tertiary amines **1t** and **1u** have been synthesized and tested in our reaction. As displayed in Scheme 3, when amine

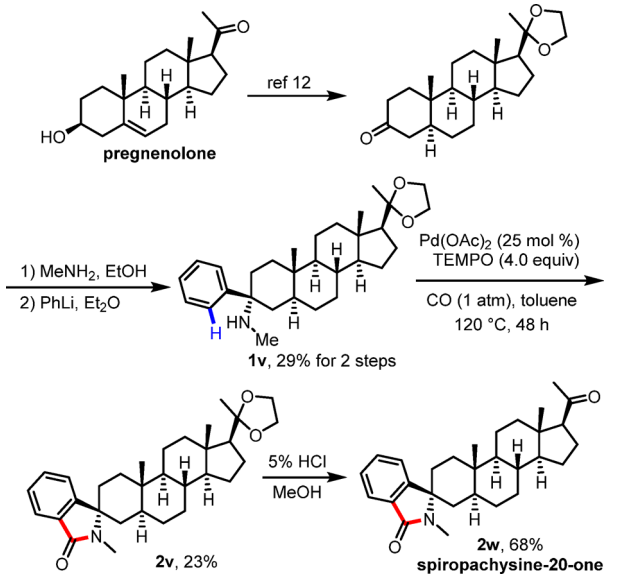
Scheme 3. Intramolecular Competitive Experiments



1t was subjected to the standard conditions, the carbonylation occurred preferentially at the more steric ally hindered aryl C−H bond to afford isoindolin-1-one **2t** as the major product in 49% yield, while the six-membered isoquinolin-1-one **3t** was obtained in only 29% yield (eq 1, Scheme 3). Moreover, when the side chain was prolonged to reduce the reactivity, the more sterically hindered C−H bond on the phenyl ring of **1u** was carbonylated with excellent regioselectivity, furnishing isoindolin-1-one **2u** as the sole product at 90% yield (eq 2). Different from the report of Garcia and Granell,[7] these results clearly indicate that the more sterically hindered reaction site was preferred in our catalytic system.

To demonstrate the synthetic application and prospects of this transformation, we next attempted to use it as the key step for the first total synthesis of the natural alkaloid spiropachysin-20-one, which was isolated from *Pachysandra terminalis*.[10] While the only known method to make spiropachysin-20-one was derivation from spiropachysine,[11] it was speculated that the construction of the spiro-lactam skeleton was the possible problem. We envisioned that this skeleton could be efficiently made using our catalytic reaction. As shown in Scheme 4, pregnane-3,20-dione, cyclic 20-(1,2-

Scheme 4. Concise Synthesis of Spiropachysin-20-one



ethanediyl acetal) **4** was synthesized from the commercially available pregnenolone via a known approach.[12] The carbonyl group was transformed to imine via condensation of methylamine, followed by attack of phenyllithium to afford steroid-derived benzylamine **1v**.[13] With our newly developed palladium-catalyzed C−H carbonylation reaction as the key step, the precursor **1v** was transferred to lactam **2v** in 23% yield. After removing the ketal protecting group under the acidic conditions, the natural product spiropachysin-20-one was finally obtained in 68% yield. Although the key step in this total synthesis afforded only relatively low yield, the first easily handled chemical synthesis of this natural product would promote its biological study.

In summary, a Pd-catalyzed C(sp^2)−H carbonylation of sterically hindered α,α-disubstituted benzylamines under 1 atm of CO for the facile synthesis of 3,3-disubstituted isoindolin-1-one has been developed in which TEMPO was used as the crucial sole oxidant. The synthetic utility of this transformation has been demonstrated by the concise total synthesis of natural product spiropachysin-20-one. Further studies using this strategy to construct other heterocyclic ring systems and to obtain the total synthesis of more biologically active complex molecules are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02856.

Experimental materials and procedures and NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Brown, H. C. *Acc. Chem. Res.* **1969**, *2*, 65. (b) Murai, S.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 837. (c) Milstein, D. *Acc. Chem. Res.* **1988**, *21*, 428. (d) Brunet, J.-J.; Chauvin, R. *Chem. Soc. Rev.* **1995**, *24*, 89. (e) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (f) Khumtaveeporn, K.; Alper, H. *Acc. Chem. Res.* **1995**, *28*, 414. (g) Drent, E.; Budzelaar, P. H. M. *Chem. Rev.* **1996**, *96*, 663. (h) Chatani, N.; Murai, S. *Synlett* **1996**, *1996*, 414. (i) Ryu, I.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1050. (j) Ryu, I. *Chem. Soc. Rev.* **2001**, *30*, 16. (k) Kiss, G. *Chem. Rev.* **2001**, *101*, 3435. (l) Church, T. L.; Getzler, Y. D. Y. L.; Byrne, C. M.; Coates, G. W. *Chem. Commun.* **2007**, 657. (m) Barnard, C. F. *Organometallics* **2008**, *27*, 5402. (n) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114. (o) Lee, H.-W.; Kwong, F.-Y. *Eur. J. Org. Chem.* **2010**, *2010*, 789. (p) Romão, C. C.; Blättler, W. A.; Seixas, J. D.; Bernardes, G. J. L. *Chem. Soc. Rev.* **2012**, *41*, 3571. (q) Wu, X.-F.; Fang, X.; Wu, L.; Jackstell, R.; Neumann, H.; Beller, M. *Acc. Chem. Res.* **2014**, *47*, 1041. (r) Wang, Y.; Yu, Z.-X. *Acc. Chem. Res.* **2015**, *48*, 2288. (s) Ambrosi, A.; Denmark, S. E. *Angew. Chem., Int. Ed.* **2016**, *55*, 12164. (t) Li, Y.; Hu, Y.; Wu, X.-F. *Chem. Soc. Rev.* **2018**, *47*, 172. (u) Peng, J.-B.; Wu, X.-F. *Angew. Chem., Int. Ed.* **2018**, *57*, 1152.

(2) (a) Liu, Q.; Zhang, H.; Lei, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 10788. (b) Liu, B.; Hu, F.; Shi, B.-F. *ACS Catal.* **2015**, *5*, 1863.

(3) Fujiwara, Y.; Kawauchi, T.; Taniguchi, H. *J. Chem. Soc., Chem. Commun.* **1980**, 220.

(4) (a) Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14082. (b) Houlden, C. E.; Hutchby, M.; Bailey, C. D.; Ford, J. G.; Tyler, S. N. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem., Int. Ed.* **2009**, *48*, 1830. (c) Lu, Y.; Leow, D.; Wang, X.; Engle, K. M.; Yu, J.-Q. *Chem. Sci.* **2011**, *2*, 967. (d) Wrigglesworth, J. W.; Cox, B.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Org. Lett.* **2011**, *13*, 5326. (e) Ma, B.; Wang, Y.; Peng, J.; Zhu, Q. *J. Org. Chem.* **2011**, *76*, 6362. (f) Lee, T.-H.; Jayakumar, J.; Cheng, C.-H.; Chuang, S.-C. *Chem. Commun.* **2013**, *49*, 11797. (g) Luo, S.; Luo, F.-X.; Zhang, X.-S.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2013**, *52*, 10598. (h) Liang, D.; He, Y.; Zhu, Q. *Org. Lett.* **2014**, *16*, 2748. (i) Shin, S.; Jeong, Y.; Jeon, W. H.; Lee, P. H. *Org. Lett.* **2014**, *16*, 2930. (j) Liu, B.; Jiang, H.-Z.; Shi, B.-F. *Org. Biomol. Chem.* **2014**, *12*, 2538. (k) Ji, F.; Li, X.; Wu, W.; Jiang, H. *J. Org. Chem.* **2014**, *79*, 11246. (l) Li, W.; Duan, Z.; Zhang, X.; Zhang, H.; Wang, M.; Jiang, R.; Zeng, H.; Liu, C.; Lei, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 1893. (m) Wang, Y.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2015**, *54*, 2255. (n) Xu, Y.; Hu, W.; Tang, X.; Zhao, J.; Wu, W.; Jiang, H. *Chem. Commun.* **2015**, *51*, 6843. (o) Wang, P.-L.; Li, Y.; Ma, L.; Luo, C.-G.; Wang, Z.-Y.; Lan, Q.; Wang, X.-S. *Adv. Synth. Catal.* **2016**, *358*, 1048. (p) Zhang, L.; Wang, C.; Han, J.; Huang, Z.-B.; Zhao, Y. *J. Org. Chem.* **2016**, *81*, 5256. (q) Wang, Y.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2017**, *56*, 3191. For amine-directed C(sp^2)−H carbonylation, see: (r) Guan, Z.-H.; Chen, M.; Ren, Z.-H. *J. Am. Chem. Soc.* **2012**, *134*, 17490. (s) Liang, D.; Hu, Z.; Peng, J.; Huang, J.; Zhu, Q. *Chem. Commun.* **2013**, *49*, 173. (t) Rajeshkumar, V.; Lee, T.-H.; Chuang, S.-C. *Org. Lett.* **2013**, *15*, 1468. (u) Chen, M.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *J. Org. Chem.* **2015**, *80*, 1258. (v) Li, W.; Duan, Z.; Jiang, R.; Lei, A. *Org. Lett.* **2015**, *17*, 1397. (w) Feng, M.; Tang, B.; Xu, H.-X.; Jiang, X. *Org. Lett.* **2016**, *18*, 4352. (x) Shi, R.; Lu, L.; Xie, H.; Yan, J.; Xu, T.; Zhang, H.; Qi, X.; Lan, Y.; Lei, A. *Chem. Commun.* **2016**, *52*, 13307. (y) Shi, R.; Niu, H.; Lu, L.; Lei, A. *Chem. Commun.* **2017**, *53*, 1908.

(5) Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Tokuda, M. *J. Am. Chem. Soc.* **2004**, *126*, 14342.

(6) Orito, K.; Miyazawa, M.; Nakamura, T.; Horibata, A.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Yamazaki, T.; Tokuda, M. *J. Org. Chem.* **2006**, *71*, 5951.

(7) (a) López, B.; Rodriguez, A.; Santos, D.; Albert, J.; Ariza, X.; Garcia, J.; Granell, J. *Chem. Commun.* **2011**, *47*, 1054. (b) Albert, J.; Ariza, X.; Calvet, T.; Font-Bardia, M.; Garcia, J.; Granell, J.; Lamela, A.; López, B.; Martinez, M.; Ortega, L.; Rodriguez, A.; Santos, D. *Organometallics* **2013**, *32*, 649. (c) Taneda, H.; Inamoto, K.; Kondo, Y. *Org. Lett.* **2016**, *18*, 2712.

(8) Haffemayer, B.; Gulias, M.; Gaunt, M. J. *Chem. Sci.* **2011**, *2*, 312.

(9) Wang, P.-L.; Li, Y.; Wu, Y.; Li, C.; Lan, Q.; Wang, X.-S. *Org. Lett.* **2015**, *17*, 3698.

(10) Zhai, H.-Y.; Zhao, C.; Zhang, N.; Jin, M.-N.; Tang, S.-A.; Qin, N.; Kong, D.-X.; Duan, H.-Q. *J. Nat. Prod.* **2012**, *75*, 1305.

(11) Kikuchi, T.; Nishinaga, T.; Inagaki, M.; Niwa, M.; Kuriyama, K. *Chem. Pharm. Bull.* **1975**, *23*, 416.

(12) (a) Hitchin, J. R.; Hamilton, N. M.; Jordan, A. M.; Lyons, A. J.; Ogilvie, D. J. *Tetrahedron Lett.* **2012**, *53*, 2868. (b) Hamilton, N. M.; Dawson, M.; Fairweather, E. E.; Hamilton, N. S.; Hitchin, J. R.; James, D. I.; Jones, S. D.; Jordan, A. M.; Lyons, A. J.; Small, H. F.; Thomson, G. J.; Waddell, I. D.; Ogilvie, D. J. *J. Med. Chem.* **2012**, *55*, 4431.

(13) The NMR spectrum of **2w** was in agreement with that of ref 11. To further infer the stereochemistry of the newly constructed quaternary carbon, benzylamine **1v** can also be gained via Ellman's protocol: McMahon, J. P.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 1645. For details, see the Supporting Information.

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