Palladium-Catalyzed Double Activation and Arylation of 2° and 3° C(sp^3)–H Bonds of the Norbornane System: Formation of a C–C Bond at the Bridgehead Carbon and Bridgehead Quaternary Stereocenter

Ramarao Parella, Srinivasarao Arulananda Babu*

Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Mohali, Manauli P.O., Sector 81, SAS Nagar, Mohali, Knowledge City, Punjab 140306, India
Fax +91(172)2240266; E-mail: sababu@iisermohali.ac.in

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Abstract: Pd-catalyzed activation and direct arylation of both 2° and the bridgehead 3° (sp^3) C–H bonds and an unprecedented C–C bond formation at the bridgehead carbon of the norbornane system are reported. The assembly of bridgehead-substituted norbornane frameworks having contiguous stereocenters was accomplished. X-ray crystal structure analysis of representative molecules unambiguously established the stereochemistry.

Key words: arylation, bridgehead substitution, C–H activation, diastereoselectivity, palladium, stereoselective synthesis

The chemistry of bridgehead-substituted bridged bicyclic frameworks (bridged rings) has a long and esteemed history.[1,2] Notably, functional group transformation at a bridged center and the generation of an quaternary bridgehead carbon of bridged bicyclic compounds is among the most challenging and fascinating of research topics. There has been a substantial number of studies on reactions at the bridgehead center of several bridged bicyclic systems.[1,2] Apart from the celebrated substitution reactions at the bridgehead carbon of bridged bicyclic compounds, there exist versatile routes[1,2] that can be used to assemble bridgehead-substituted bicyclic frameworks, including bridgehead enolate chemistry[1i,j] and Diels–Alder reaction.[1a–h]

The development of novel C–C bond-forming protocols and functionalization of organic molecules with stereocontrol are persistent goals of organic chemists. In recent years, transition-metal-catalyzed, and especially Pd-catalyzed functionalization of C–H bonds has emerged as a powerful tool in organic synthesis.[3–6] In this context, the Pd-catalyzed, auxiliary-aided C–H functionalization of sp^3 C–H bonds initiated by Daugulis, Yu, and other groups is evolving as a very convenient tactic.[3–6] Excellent papers on the Pd-catalyzed, auxiliary-directed C–H activation of 1° and 2° sp^3 C–H bonds have been published. Recently, we reported an auxiliary-enabled, Pd-catalyzed direct C–H arylation of 2° sp^3 C–H bonds of small rings such as cyclopropane and cyclobutane.[4k,l] To the best of our knowledge only a few reports exist that deal with metal-catalyzed C–H functionalization of 3° sp^3 C–H bonds.[6]

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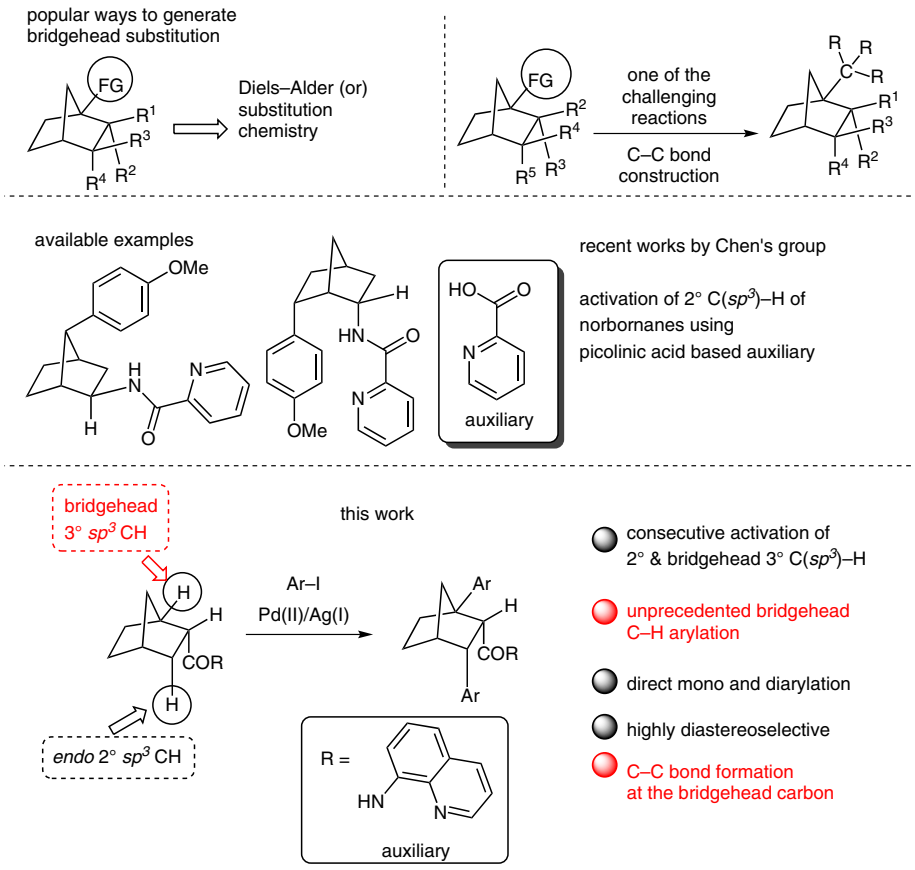
In light of the above developments, we wanted to examine one of the most challenging reactions of organic chemistry, 'bridgehead-substitution' via C–H activation of the bridgehead 3° C(sp^3)–H bond of norbornane systems. To the best of our knowledge there is only one report[3k] dealing with two examples related to the C–H functionalization of bridgehead 3° C(sp^3)–H bonds of the norbornane-type systems. The direct arylation of the bridgehead 3° C(sp^3)–H bond of norbornanes, using 8-aminoquinoline and 2-thiomethylaniline as auxiliaries, which were developed by Daugulis, form the basis of this work. Herein, we report an auxiliary-aided, Pd-catalyzed sequential activation and arylation of 2° C(sp^3)–H and the bridgehead 3° C(sp^3)–H bonds and an unprecedented C–C bond formation at the bridgehead carbon of the norbornane framework (Scheme 1).

To examine the C–H functionalization of 2° C(sp^3)–H bonds and 'bridgehead substitution' via C–H activation of the bridgehead 3° C(sp^3)–H bond, we prepared substrate *endo*-*N*-(quinolin-8-yl)bicyclo[2.2.1]heptane-2-carboxamide (**1a**) from *endo*-bicyclo[2.2.1]heptane-2-carboxylic acid and an auxiliary (e.g., 8-aminoquinoline). To arrive at the best reaction conditions and solvents, we then performed a series of reactions, listed in Table 1, that involved Pd-catalyzed C–H arylation of the substrate **1a** (*endo*) with 1-iodo-4-methylbenzene (**2a**). The reaction of a mixture of substrate **1a** (*endo*), aryl iodide **2a** and AgOAc, either in the presence or absence of the $Pd(OAc)_2$ catalyst (10 mol%), in toluene at 110 °C did not give the product in good yield (Table 1, entries 1 and 2). We next performed the C–H arylation of substrate **1a** with **2a** in the presence of Ag_2CO_3 as a halide-removing agent, instead of AgOAc, in toluene at 110 °C. In this reaction, we were pleased to observe the formation of product **3a** (65%; Table 1, entry 3) via the direct bis-arylation of both 2° C(sp^3)–H (*endo*) and the bridgehead 3° C(sp^3)–H bonds and an unprecedented C–C bond formation at the bridgehead center of the norbornane system **1a**.

The C–H functionalization of substrate **1a** with 1-iodo-4-methylbenzene (**2a**) in the presence of Ag_2CO_3 and $Pd(OAc)_2$ catalyst (10 mol%) in *tert*-butanol gave the product **3a** with slightly improved yield (70%; Table 1, entry 4). When only 5 mol% $Pd(OAc)_2$ catalyst was used, product **3a** was obtained in 60% yield (Table 1, entry 5). The Pd-catalyzed C–H arylation of **1a** with **2a** in the presence of various additives such as K_2CO_3, Na_2CO_3, KOAc,



Scheme 1 Theme of this work

and $PhI(OAc)_2$ gave product **3a** in 24–30% yields (Table 1, entries 6–9). Use of other palladium catalysts such as $PdCl_2$, $Pd(TFA)_2$, $Pd(MeCN)_2Cl_2$ and $Pd(PPh_3)_4$ were ineffective (Table 1, entries 10–13). The reaction of **1a** with **2a** in the presence of Ag_2CO_3 and the $Pd(OAc)_2$ catalyst (10 mol%) in other solvents such as MeCN, 1,2-DCE, 1,4-dioxane, EtOH, AcOH, and *tert*-amyl alcohol failed to afford product **3a** with improved yields (Table 1, entries 14–19). The Pd-catalyzed C–H arylation of substrate **1a** with bromobenzene (**2b**) or chlorobenzene (**2c**) did not furnish any product (Table 1, entries 20 and 21).

Under the optimized reaction conditions (Table 1, entries 3 and 4), the Pd-catalyzed Ag-promoted C–H arylation of **1a** (1 equiv) with 1-iodo-4-methylbenzene (**2a**; 4 equiv) afforded product **3a** through the direct bis-arylation of both 2° C(sp^3)–H (*endo*) and bridgehead 3° C(sp^3)–H bonds of the norbornane framework of **1a**. Realistically, under the experimental conditions, one would expect the formation of both the mono- and bis-arylated products **4a**, **4a′**, and **3a** (Table 1). However, we did not observe either of the monoarylated products **4a** or **4a′** under the reaction conditions shown in Table 1.

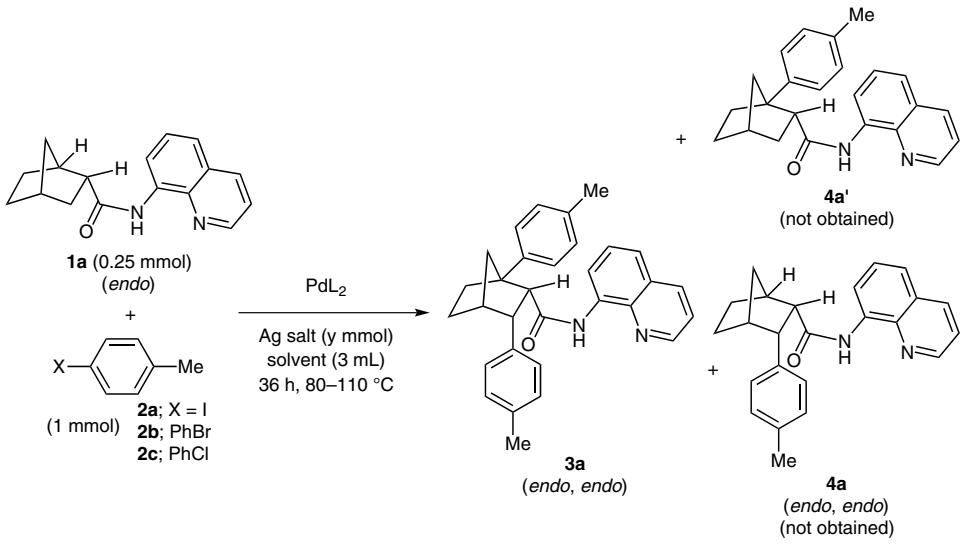
We decided to study further the reaction conditions and determine the number of equivalents of aryl iodide required to produce only the monoarylated product **4a** or **4a′** (Scheme 2).[7b] By employing 2–4 equivalents of 1-iodo-4-methylbenzene (**2a**) in the Pd-catalyzed C–H functionalization of substrate **1a**, only the bisarylated product **3a** (Scheme 2, entries 1–3) was observed. The reaction of substrate **1a** with 1.5 equivalent of aryl iodide (**2a**) gave bisarylated product **3a** (6%) and monoarylated product **4a** (40%; Scheme 2, entry 4). The reaction of substrate **1a** with 1.0 or 0.5 equivalent of 1-iodo-4-methylbenzene (**2a**) in *tert*-butanol selectively gave the monoarylated norbornane system **4a** in 57 and 32% yield, respectively (Scheme 2, entries 5 and 6). In these reactions, we did not get the other expected product **4a′**, which convincingly indicated that arylation of the 2° C(sp^3)–H bond is easier than the bridgehead 3° C(sp^3)–H bond of norbornanes.

We then extended the scope of this protocol by exploiting the optimized reaction conditions that provided the selective formation of the monoarylated compound **4a** (Scheme 2, entry 5). We performed several reactions using a range of aryl iodides as the coupling partner in the Pd-catalyzed, auxiliary-aided selective C–H arylation of the 2° C(sp^3)–H (*endo*) bond of the norbornane system **1a**, which gave the corresponding monoarylated norbornane frameworks **4b–f** in 49–73% yield (Scheme 2) with a high degree of stereoselectivity.

The above reactions involving substrate **1a** indicated that the auxiliary, 8-aminoquinoline, attached to the norbornane system assists in the Pd-catalyzed dual activation of both 2° C(sp^3)–H (*endo*) and the bridgehead 3° C(sp^3)–H bonds of substrate **1a**. Under the optimized reaction con-

ditions, the C–H arylation of other substrates **1b**–**h**, prepared by using various substrates and auxiliaries, were ineffective (Scheme 3). The reason for this may be that the respective auxiliaries attached to the norbornane system did not direct the C–H activation of the norbornane ring. The arylation of norbornene system **1f**,[7a] which is struc-

Table 1 Optimization of Reaction Conditions



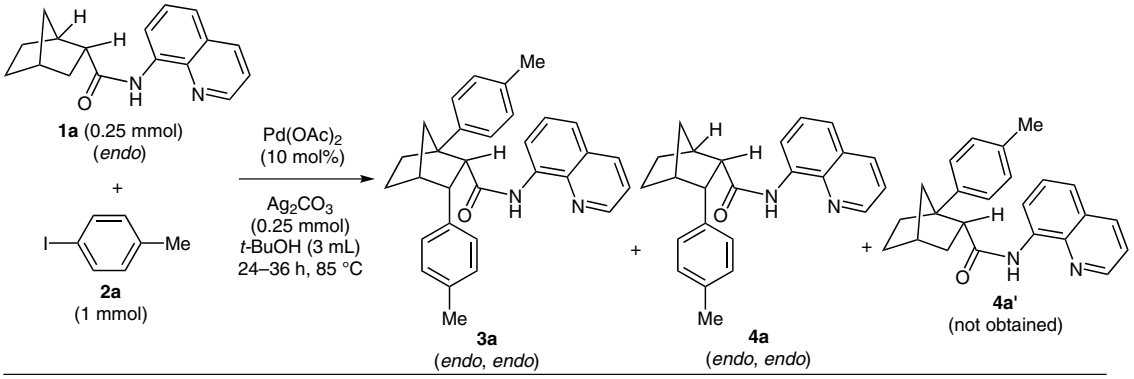
Entry	Catalyst (mol%)	Oxidant/halide removing agent (y mmol)	Solvent	Temp (°C)	Yield of **3a** (%)
1	none	AgOAc (0.55)	toluene	110	0
2	$Pd(OAc)_2$ (10)	AgOAc (0.55)	toluene	110	5
3	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.25)	toluene	110	65
4	**$Pd(OAc)_2$ (10)**	**Ag_2CO_3 (0.25)**	***t*-BuOH**	**85**	**70**
5	$Pd(OAc)_2$ (5)	Ag_2CO_3 (0.25)	*t*-BuOH	85	60
6	$Pd(OAc)_2$ (10)	K_2CO_3 (0.25)	*t*-BuOH	85	0
7	$Pd(OAc)_2$ (10)	Na_2CO_3 (0.25)	*t*-BuOH	85	0
8	$Pd(OAc)_2$ (10)	KOAc (0.25)	*t*-BuOH	85	24
9	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (0.25)	*t*-BuOH	85	30
10	$PdCl_2$ (10)	Ag_2CO_3 (0.25)	*t*-BuOH	85	25
11	$Pd(TFA)_2$ (10)	Ag_2CO_3 (0.25)	*t*-BuOH	85	26
12	$Pd(CH_3CN)_2Cl_2$ (10)	Ag_2CO_3 (0.25)	*t*-BuOH	85	0
13	$Pd(PPh_3)_4$ (10)	Ag_2CO_3 (0.25)	*t*-BuOH	85	0
14	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.25)	MeCN	80	11
15	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.25)	1,2-DCE	80	9
16	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.25)	1,4-dioxane	100	15
17	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.25)	EtOH	80	54
18	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.25)	AcOH	110	0
19	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.25)	*t*-AmylOH	100	40
20[a]	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.25)	*t*-BuOH	85	0
21[b]	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.25)	*t*-BuOH	85	0

[a] 1-Bromobenzene (**2b**) was used instead of **2a**; the corresponding product was not obtained.
[b] 1-Chlorobenzene (**2c**) was used instead of **2a**; the corresponding product was not obtained.

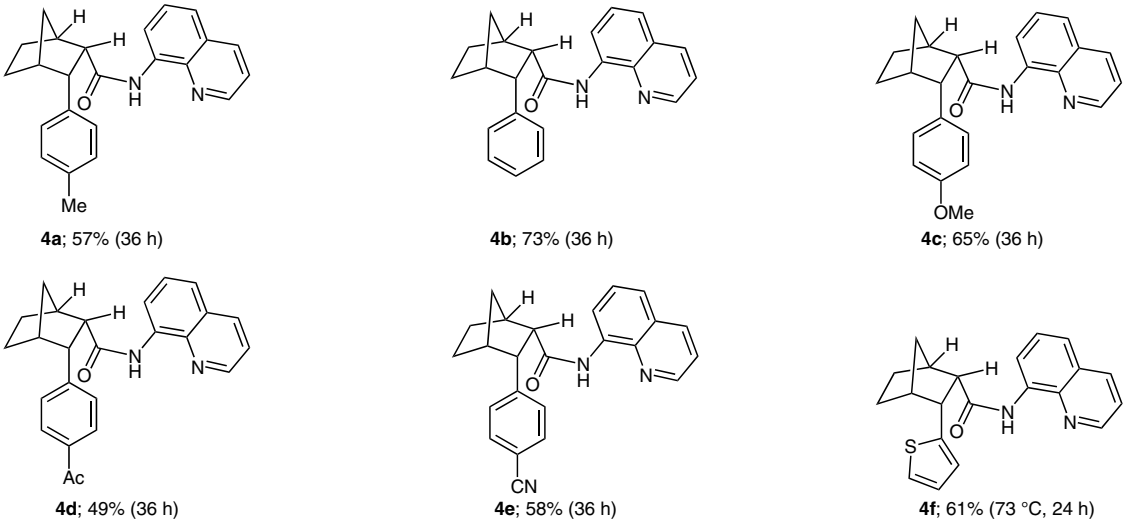
turally similar to the substrate **1a**, did not furnish any new product under the experimental conditions. The use of **1h**, which is similar to substrate **1a**, in the Pd-catalyzed C–H arylation reaction also failed to afford any arylated product. We are investigating new reactions using these substrates and the results will be published in due course.

To develop other working auxiliaries attached to the norbornane framework, we then carried out Pd-catalyzed arylation of substrate **1i** (*endo*), prepared from an auxiliary [e.g., 2-(methylthio)aniline] with various aryl iodides (Scheme 4). By employing the optimized reaction conditions, the Pd-catalyzed selective C–H activation and arylation of an *endo* 2° C(sp^3)–H bond of substrate **1i** gave the monoarylated norbornane systems **6a**–**c** in 32–36% yield with high stereoselectivity (Scheme 4).[7b] The yields of the products **6a**–**c** were lower than the products **4a**–**f**, which is perhaps due to the difference in the abilities of the respective auxiliaries (attached to the substrates **1i** and **1a**) to assist the Pd-catalyzed C–H activation reactions.

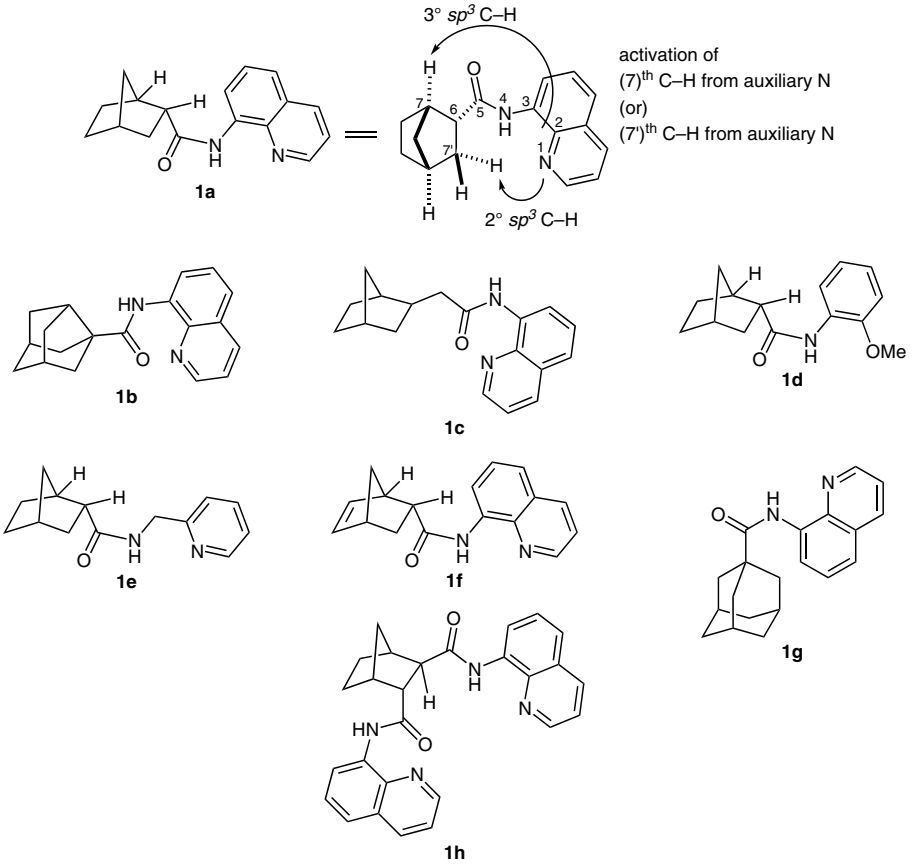
The generality and scope of this protocol involving the Pd-catalyzed, auxiliary-directed activation and direct arylation of 2° and bridgehead 3° C(sp^3)–H bonds and an unprecedented C–C bond formation at the bridgehead center of the norbornane system were elaborated (Scheme 5). Under the optimized reaction conditions, the production of a wide range bisarylated norbornane frameworks **3a**–**g** (45–81%) and **5a**–**g** (23–50%) from the direct arylation of 2° C(sp^3)–H (*endo*) and bridgehead 3° C(sp^3)–H bonds of substrates **1a** and **1i** was accomplished by employing several substituted aryl iodides containing electron-withdrawing or electron-donating groups (Scheme 5).[7b,8–10] Double heterocyclic substitutions on the norbornane system **1a** through direct C–H functionalization using 2-iodothiophene, successfully gave the expected product **3h** (78%; Scheme 5). All the reactions furnished the products **3a**–**h** and **5a**–**g** as single diastereomers through selective incorporation of various aryl groups at the *endo* 2° C(sp^3)–H and bridgehead 3° C(sp^3)–H positions of the



entry	**1a** (mmol)	**2a** (mmol)	ratio **1a**:**2a**	**3a** yield (%)	**4a** yield (%)
1	0.25	1.0	1:4	70	0
2	0.25	0.75	1:3	50	0
3	0.25	0.5	1 : 2	36	0
4	0.25	0.375	1:1.5	6	40
5	0.25	0.25	1:1	0	57
6	0.25	0.125	1:0.5	0	32



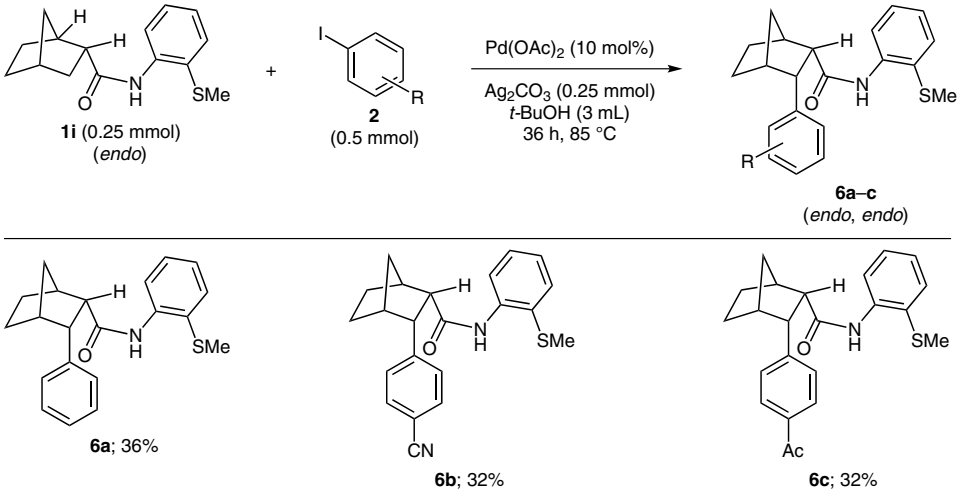
Scheme 2 Mono- and bis-C–H functionalization of **1a**



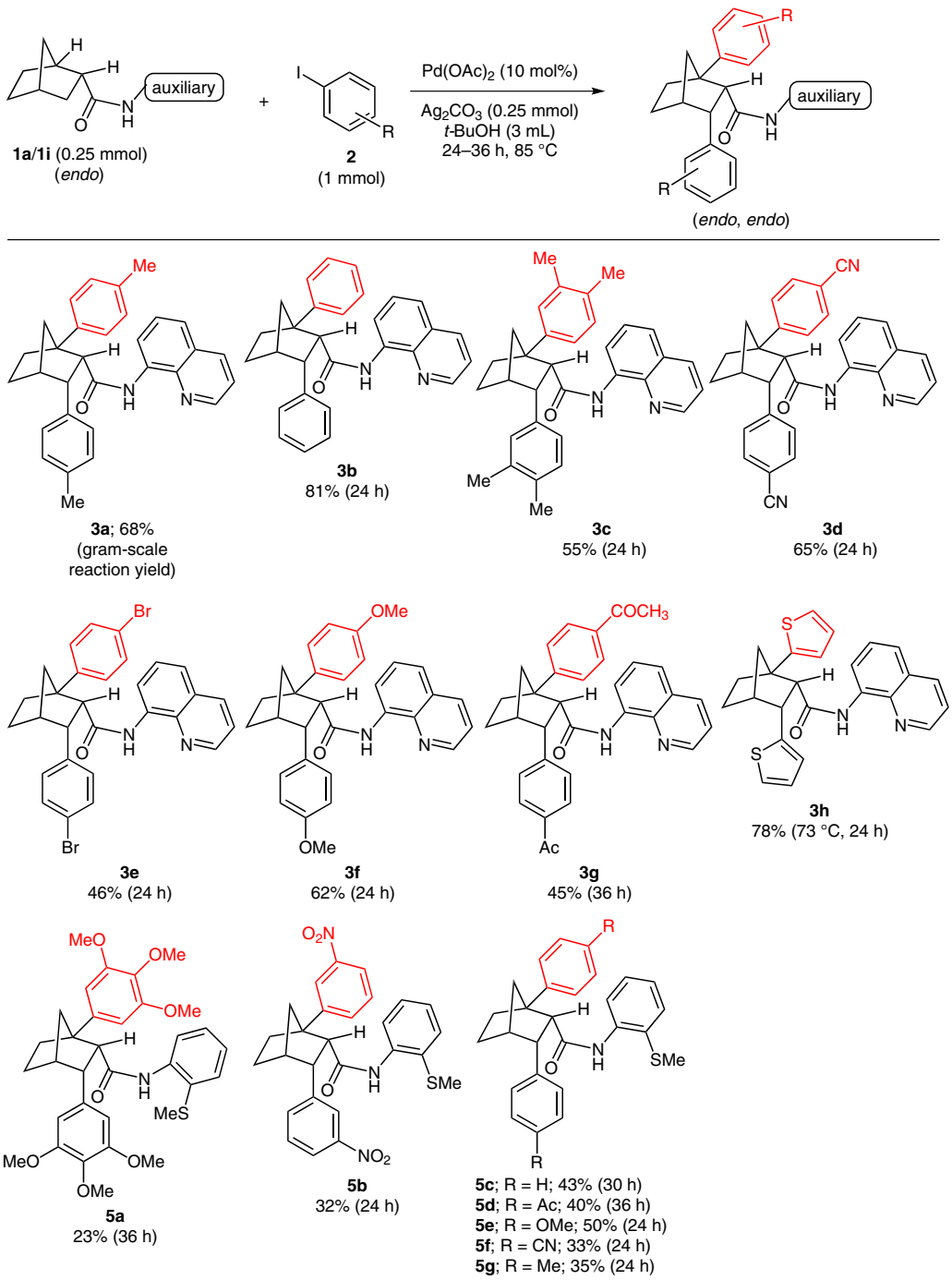
Scheme 3 The role of the auxiliary and other bicyclic compounds

norbornane systems **1a** and **1i**. The stereochemistry of representative products **4a**, **3d**, **5d**, and **7b** were assigned on the basis of X-ray crystal structure analysis (Figure 1).[7b,11]

In the reactions shown in the Table 1, Scheme 2, and Scheme 5 (products **3a**–**h** and **5a**–**g**), similar aryl groups were incorporated at the *endo* 2° C(sp^3)–H as well as at the bridgehead 3° C(sp^3)–H positions of the norbornane systems **1a** and **1i**. Therefore, we envisaged the introduction of a different aryl group at the bridgehead carbon and examined the prospect of this unprecedented 'bridgehead carbon substitution' via C–H activation (Scheme 6).[7b] To this end, we carried out a series of reactions with the aim of achieving exclusive activation of the bridgehead 3° C(sp^3)–H bond and C–C bond formation at the bridgehead carbon.



Scheme 4 Mono C–H arylation of the 2° C(sp^3)–H (*endo*) bond of the norbornane framework of **1i**



Scheme 5 Double C–H arylation of norbornanes **1a** and **1i**

We treated several *endo* substituted norbornane systems, with the generalized structure **4**, with a variety of aryl iodides and heteroaryl iodide (Scheme 6). These reactions successfully gave the respective novel bridgehead-arylated norbornane systems **7a**–**h** (32–50%) through C–H activation of the bridgehead 3° C(sp^3)–H bond followed by C–C bond formation at the bridgehead carbon. The products **7a**–**h** were obtained in low to moderate yields, which suggested that the C–H functionalization of the bridgehead 3° C(sp^3)–H bond is a relatively difficult reaction.

In summary, we have presented our work on the Pd-catalyzed concurrent activation and arylation of 2° and bridgehead 3° C(sp^3)–H bonds of norbornane systems and an unprecedented ‘formation of C–C bond at the bridgehead carbon and bridgehead quaternary stereocenter via the C–H activation’. Novel bridgehead-substituted norbornane frameworks having contiguous stereocenters were assembled. Further work is in progress to demonstrate the utility of this protocol.

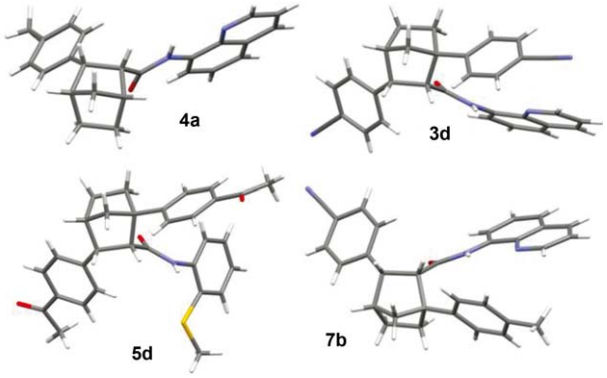


Figure 1 X-ray crystal structures of products **4a**, **3d**, **5d** and **7b**

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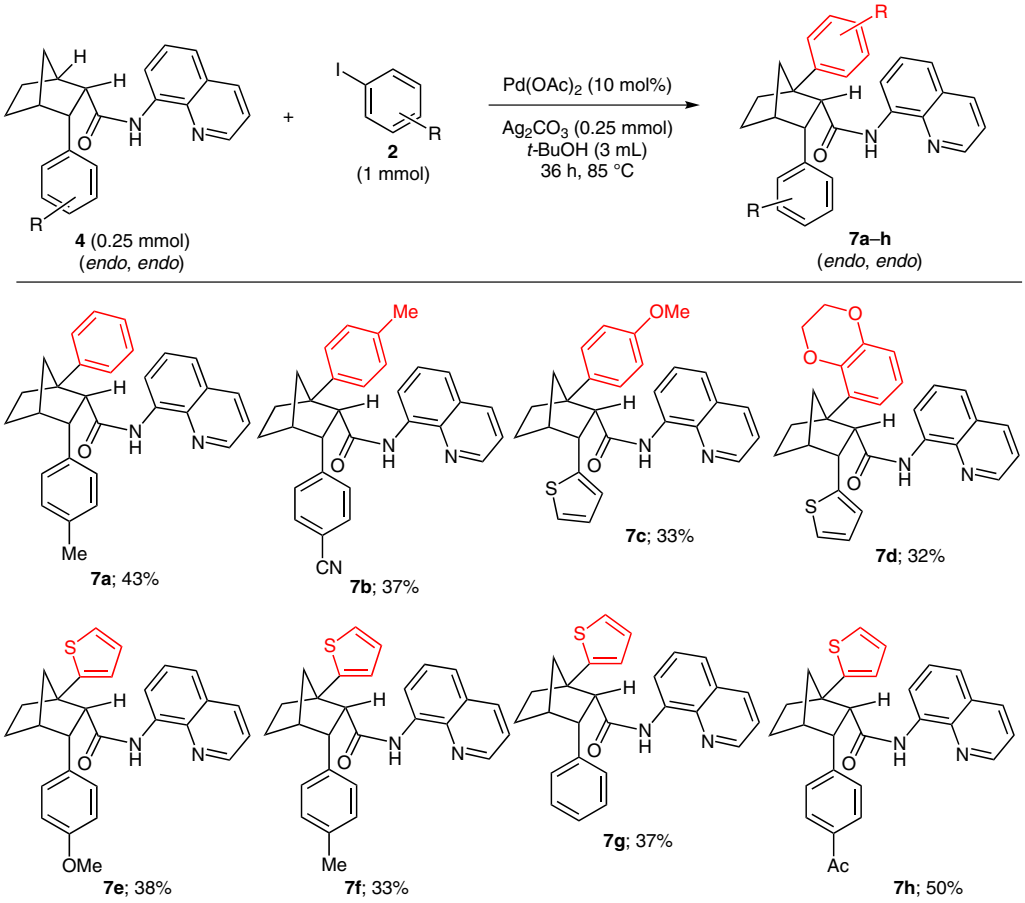
References and Notes

(1) (a) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 5th ed., Vols. 1 and 2; Springer: New York, **2007**. (b) Warrener, R. N. *Eur. J. Org. Chem.* **2000**, 3363. (c) Bear, B. R.; Sparks, S. M.; Shea, K. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 820. (d) Jiang, Y.; Chen, C.-F. *Eur. J. Org. Chem.* **2011**, 6377. (e) Fringuelli, F.; Taticchi, A. *The Diels–Alder Reaction: Selected Practical Methods*; Wiley: New York, **2002**. (f) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 1668. (g) Liao, C.-C.; Peddinti, R. K. *Acc. Chem. Res.* **2002**, *35*, 856. (h) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem. Int. Ed.* **2000**, *39*, 44. (i) Simpkins, N. S. *Chem. Commun.* **2013**, *49*, 1042. (j) Hayes, C. J.; Simpkins, N. S.; Kirk, D. T.; Mitchell, L.; Baudoux, J.; Blake, A. J.; Wilson, C. *J. Am. Chem. Soc.* **2009**, *131*, 8196. (k) Csende, F.; Fulop, F.; Stajer, G. *Curr. Org. Synth.* **2008**, *5*, 173. (l) Butkus, E. *Synlett* **2001**, 1827. (m) Wang, Z. *Synlett* **2012**, 2311. (n) Njardarson, J. T. *Tetrahedron* **2011**, *23*, 7631. (o) Brown, H. C. *Acc. Chem. Res.* **1973**, *6*, 377. (p) Presset, M.; Coquerel, Y.; Rodriguez, J. *Chem. Rev.* **2013**, *113*, 525. (q) Ruiz, M.; López-Alvarado, P.; Giorgi, G.; Menéndez, J. C. *Chem. Soc. Rev.* **2011**, *40*, 3445.

(2) (a) Kraus, G. A.; Hon, Y.-S.; Thomas, P. J.; Laramay, S.; Liras, S.; Hanson, J. *Chem. Rev.* **1989**, *89*, 1591. (b) Paquette, L. A. *Chem. Soc. Rev.* **1995**, *24*, 9. (c) Harmata, M.; Wacharasindhu, S. *Synthesis* **2007**, 23. (d) Wendeborn, S.; Nussbaumer, H.; Schaetzer, J.; Winkler, T. *Synlett* **2010**, 1966. (e) Grimme, W.; Bertsch, A.; Flock, H.; Noack, T.;



Scheme 6 C–H arylation of the bridgehead C–H bond of **4**

Krauthäuser, S. *Synlett* **1998**, 1175. (f) Slowinski, F.; Ayad, O. B.; Vache, J.; Saady, M.; Leclerc, O.; Lochead, A. *Org. Lett.* **2010**, *12*, 5004. (g) Aubé, J.; Szostak, M. *Chem. Rev.* **2013**, *113*, 5701. (h) Coombs, T. C.; Zhang, Y.; Garnier-Amblard, E. C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2009**, *131*, 876. (i) Takeuchi, K.; Ohga, Y. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 833. (j) Wiberg, K. B.; Lowry, B. R. *J. Am. Chem. Soc.* **1963**, *85*, 3188. (k) Bartlett, P. D.; Knox, L. H. *J. Am. Chem. Soc.* **1939**, *61*, 3184. (l) Yates, P.; Kaldas, M. *Can. J. Chem.* **1992**, *70*, 1492. (m) Gohlke, R. S. *J. Am. Chem. Soc.* **1968**, *90*, 2714.

(3) For selected articles, see: (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. For selected review articles, see: (c) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (d) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094. (e) Rouquet, G.; Chatani, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 11726. (f) Davies, H. M. L.; Du Bois, J.; Yu, J.-Q. *Chem. Soc. Rev.* **2011**, *40*, 1855. (g) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (h) Wu, Y.; Wang, J.; Mao, F.; Kwong, F. Y. *Chem. Asian J.* **2014**, *9*, 26. (i) Zhu, C.; Wang, R.; Falck, J. R. *Chem. Asian J.* **2012**, *7*, 1502. (j) Zhong, Y.; Loh, K. *Chem. Asian J.* **2010**, *5*, 1532. (k) Ren, Z.; Mo, F.; Dong, G. *J. Am. Chem. Soc.* **2012**, *134*, 16991.

(4) For selected reviews, see: (a) Li, H.; Li, B.-J.; Shi, Z.-J. *Catal. Sci. Technol.* **2011**, *1*, 191. (b) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem. Eur. J.* **2010**, *16*, 2654. (c) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. For selected articles, see: (d) Ackermann, L.; Vicente, R.; Born, R. *Adv. Synth. Catal.* **2008**, *350*, 741. (e) Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 12984. (f) Ye, X.; He, Z.; Ahmed, T.; Weise, K.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. *Chem. Sci.* **2013**, *4*, 3712. (g) White, C. M. *Science* **2012**, *335*, 807. (h) Gutekunst, W. R.; Baran, P. S. *Angew. Chem. Int. Ed.* **2012**, *51*, 7507. (i) Roman, D. S.; Charette, A. B. *Org. Lett.* **2013**, *15*, 4394. (j) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391. (k) Parella, R.; Gopalakrishnan, B.; Babu, S. A. *J. Org. Chem.* **2013**, *78*, 11911. (l) Parella, R.; Gopalakrishnan, B.; Babu, S. A. *Org. Lett.* **2013**, *15*, 3238. (m) Santos, A. D.; El Kaïm, L.; Grimaud, L.; Ramozzi, R. *Synlett* **2012**, 438. (n) Odani, R.; Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *Heterocycles* **2014**, *88*, 595. (o) Christakakou, M.; Schön, M.; Schnürch, M.; Mihovilovic, M. D. *Synlett* **2013**, *24*, 2411. (p) Rao, Y. *Synlett* **2013**, *24*, 2472.

(5) (a) He, G.; Chen, G. *Angew. Chem. Int. Ed.* **2011**, *50*, 5192. (b) Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 2124. (c) Sun, W.-W.; Cao, P.; Mei, R.-Q.; Li, Y.; Ma, Y.-L.; Wu, B. *Org. Lett.* **2013**, *16*, 480.

(6) For examples on Pd-catalyzed 3° C(sp^3)–H activation, see: (a) Hoshiya, N.; Kobayashi, T.; Arisawa, M.; Shuto, S. *Org. Lett.* **2013**, *15*, 6202. (b) Cao, X.; Yang, W.; Liu, C.; Wei, F.; Wu, K.; Sun, W.; Song, J.; Xie, L.; Huang, W. *Org. Lett.* **2013**, *15*, 3102. (c) Saget, T.; Perez, D.; Cramer, N. *Org. Lett.* **2013**, *15*, 1354. (d) Rousseaux, S.; Liégault, B.; Fagnou, K. *Chem. Sci.* **2012**, *3*, 244. (e) Ladd, C. L.; Roman, D. S.; Charette, A. B. *Org. Lett.* **2013**, *15*, 1350.

(7) For a paper dealing with norbornene-type systems with the palladium catalyst, see: (a) Malacria, M.; Maestri, G. *J. Org. Chem.* **2013**, *78*, 1323. (b) The stereochemistry was assigned based on X-ray crystal structures of **4a**, **3d**, **5d**, and **7b** and the similarity in the NMR spectral pattern.

(8) **General procedure for the direct C–H arylation of norbornane systems and the preparation of 3a–h, 5a–g, and 7a–h:** A solution of bridged bicyclic framework **1a**, **1i** or **4** (0.25 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol%), aryl iodide (1 mmol), and Ag_2CO_3 (68.9 mg, 0.25 mmol) in anhydrous *t*-BuOH (3 mL) was heated at an appropriate temperature and for an appropriate time (73–85 °C, 24–36 h; see the respective tables or schemes for specific examples) under a nitrogen atmosphere. After the reaction period, the reaction mixture was diluted with EtOAc and concentrated in vacuum. Purification of the resulting reaction mixture by column chromatography (silica gel, 100−200 mesh) furnished the corresponding bisarylated bicyclo[2.2.1]heptane-2-carboxamides.

(9) **Analytical data of 3a:** Following the general procedure described above, **3a** was obtained after purification by column chromatography on silica gel (EtOAc–hexanes, 30:70). Yield: 70% (78 mg); brown solid; mp 172–174 °C (MeOH–hexanes, 1:1). FTIR (KBr): 3401, 1629, 1521, 1322, 667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.27 (br s, 1 H), 8.63 (dd, *J* = 7.2, 1.6 Hz, 1 H), 8.57 (dd, *J* = 4.2, 1.6 Hz, 1 H), 8.07 (dd, *J* = 8.2, 1.6 Hz, 1 H), 7.47–7.34 (m, 5 H), 7.18 (d, *J* = 8.0 Hz, 2 H), 7.09 (d, *J* = 8.0 Hz, 2 H), 7.01 (d, *J* = 8.0 Hz, 2 H), 3.88 (dd, *J* = 11.0, 2.8 Hz, 1 H), 3.57 (dd, *J* = 11.0, 1.3 Hz, 1 H), 2.90–2.85 (m, 1 H), 2.80 (br s, 1 H), 2.32 (s, 3 H), 2.30–2.26 (m, 2 H), 2.23 (s, 3 H), 1.93 (dd, *J* = 9.5, 1.6 Hz, 1 H), 1.83–1.77 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3, 147.6, 141.2, 138.2, 137.6, 136.0, 135.7, 134.9, 134.6, 129.0, 128.6, 128.2, 127.7, 127.3, 127.1, 121.3, 120.9, 116.2, 58.0, 56.2, 49.2, 46.5, 41.6, 29.6, 23.9, 21.1, 21.0. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{31}H_{31}N_2O$: 447.2436; found: 447.2444.

(10) **Analytical data of 3b:** Following the general procedure described above, **3b** was obtained after purification by column chromatography on silica gel (EtOAc–hexanes, 30:70). Yield: 81% (84 mg); white solid; mp 135–137 °C (MeOH–hexanes, 1:1). FTIR (KBr): 3300, 1668, 1587, 1321, 1021 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.30 (br s, 1 H), 8.63 (dd, *J* = 7.2, 1.9 Hz, 1 H), 8.56–8.55 (m, 1 H), 8.06 (dd, *J* = 8.3, 1.8 Hz, 1 H), 7.52–7.49 (m, 1 H), 7.46–7.07 (m, 12 H), 3.92 (dd, *J* = 13.6, 1.4 Hz, 1 H), 3.63 (dd, *J* = 13.6, 1.4 Hz, 1 H), 2.92–2.86 (m, 2 H), 2.36–2.31 (m, 2 H), 1.96 (dd, *J* = 9.4, 1.6 Hz, 1 H), 1.86–1.78 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 147.7, 144.1, 140.7, 138.2, 136.0, 134.5, 128.3, 128.1, 127.8, 127.7, 127.3, 127.2, 126.3, 125.6, 121.3, 120.9, 116.1, 58.0, 56.5, 49.5, 46.4, 41.4, 29.6, 23.8. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{29}H_{27}N_2O$: 419.2123; found: 419.2123.

(11) The crystallographic data have been deposited at the Cambridge Crystallographic Data Centre: CCDC-982495 (**4a**), CCDC-982494 (**3d**), CCDC-982496 (**5d**), and CCDC-982497 (**7b**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

