Letter

Rh(I)/NHC*-Catalyzed Site- and Enantioselective Functionalization of C(sp3)-H bonds Toward Chiral Triarylmethanes

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Rh(I)/NHC*-Catalyzed Site- and Enantioselective Functionalization of C(sp^3)–H bonds Toward Chiral Triarylmethanes

Ju Hyun Kim, Steffen Greßies, Mélissa Boultadakis-Arapinis, Constantin Daniliuc and Frank Glorius*

Organisch-Chemisches Institut Westfälische Wilhelms-Universität Münster Corrensstraße 40, 48149 Münster (Germany)

KEYWORDS: C(sp^3)–H functionalization, asymmetric arylation, triarylmethane, N-heterocyclic carbenes

ABSTRACT: The first Rh(I)-catalyzed asymmetric approach for the intermolecular functionalization of C(sp^3)–H bonds is reported. For the first time, unsymmetrical NHCs was used for asymmetric catalysis that is capable of achieving not only high site-selectivity, but also enantioselectivity. The Rh(I)/NHC* catalytic systems were applied to asymmetric direct C(sp^3)–H arylation, which provides syntheticroute towards enantioenriched triarylmethanes.

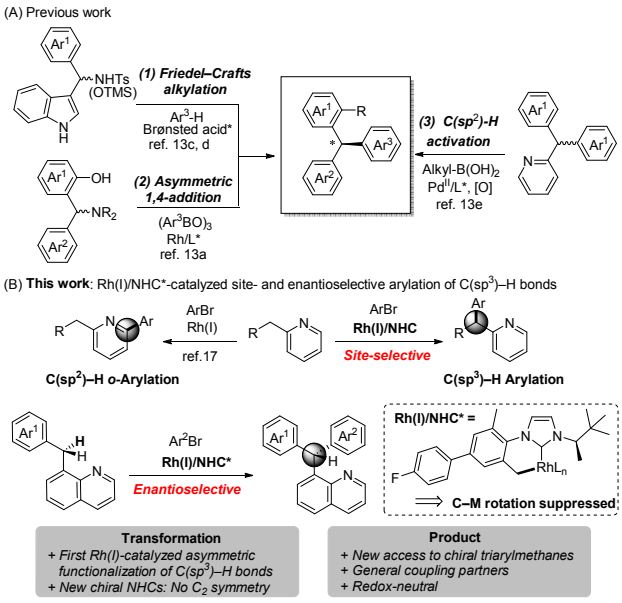
KEYWORDS: C(sp^3)–H functionalization, asymmetric arylation, triarylmethane, N-heterocyclic carbenes, rhodium

The development of transition metal-catalyzed direct functionalizations of C(sp^3)–H bonds is one of the most important subjects in modern organic chemistry in view of atom- and step-economy.[1] Despite the immense importance of this strategy, the reactivity and selectivity issues, particularly controlling the site-selectivity and enantioselectivity, remain a significant challenge.[2] In the past few years, great progress has been made in the development of catalytic asymmetric C(sp^3)–H bond functionalizations by using chiral versions of phosphoramidite, phosphine or amino acid ligands.[3] However, the majority of these examples have focused on intramolecular transformations under palladium catalysis. On the other hand, very few examples of intermolecular enantioselective functionalizations of C(sp^3)–H bonds have been reported.[4] Although Rh(II)-catalyzed asymmetric metal carbene insertions into C(sp^3)–H bonds have been well established,[5] to the best of our knowledge, other rhodium-catalyzed asymmetric methods for the intermolecular functionalization of C(sp^3)–H bonds have not been reported to date.

To overcome the tremendous challenges faced in C(sp^3)–H bond functionalization, new ligands and catalytic systems need to be developed. A number of papers have demonstrated that N-heterocyclic carbenes (NHCs) can be used as efficient ligands for the functionalization of C(sp^3)–H bonds due to strong σ-donor ability.[6] Additionally, a great advantage of employing NHC ligands is the ease of varying their steric and electronic properties.[7] Given the precedent of using the attractive features of NHC ligands,[8] we envisioned that an intermolecular asymmetric functionalization of C(sp^3)–H bonds could be achieved by using chiral NHC ligands. As a proof of concept, we first investigated a rhodium-catalyzed intermolecular arylation. The employed Rh/NHC* catalytic system controls the site- as well as enantioselectivity, which provides efficient and easy access to chiral triarylmethanes.

Triarylmethanes are important molecular frameworks in organic synthesis, medicinal chemistry, as well as in materials such as dyes and fluorescent compounds.[9] Consequently, elegant approaches to the synthesis of racemic triarylmethanes have been developed.[10] In recent years, a few asymmetric synthetic methods have been successfully developed toward enantioenriched triarylmethanes which are especially prominent in pharmaceutical applications,[11] However, most of this work is focused on stereospecific approaches.[12] In stark contrast, there are only a handful of examples reported starting from racemic compounds (Scheme 1A).[13]Further, these methods suffer from significant disadvantages such as the requirement of multistep substrate preparations, poor enantioselectivity and limited scope of substrates. In consideration of the growing interest in green and efficient process, a new approach through direct functionalization of C(sp^3)–H bonds would be highly desirable. Although Oshima[14] and Walsh[15] reported the Pd catalyzed direct arylation of diarylmethanes to form triarylmethanes, no enantioselective approach has been disclosed. The major obstacle possibly arises from the difficulty in finding suitable ligands and catalysts.[13b,15a]

Scheme 1. Synthesis of chiral triarylmethanes

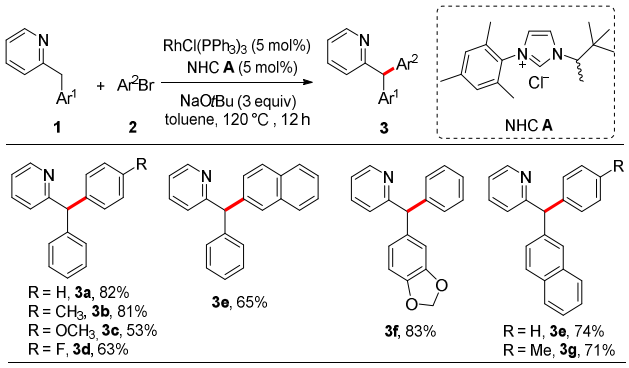


Herein, we report an operationally simple Rh(I)/NHC* catalytic system which enables direct arylations of benzylic C(sp^3)–H bonds to give triarylmethanes. Significantly, the use of the Rh(I)/NHC catalytic system can reverse the site-selectivity of pyridines under Rh(I) catalysis. Furthermore, the present catalytic system can be applied to the enantioselective functionalization of

C(sp^3)–H bonds, thus providing a novel route towards enantioenriched triarylmethanes (Scheme 1B).

In order to address the challenge associate with site-selectivity, we began our investigations by examining the direct arylation of 2-benzylpyridine (**1a**) with bromobenzene (**2a**) as the model substrates, where the reaction may occur at either an aromatic C(sp^2)-H bond[16] or a benzylic C(sp^3)–H bond. To our delight, the desired product **3a** was selectively obtained in 70% yield when the reaction was carried out in the presence of $Rh(PPh_3)_3Cl$ (5 mol%), IMes·HCl (5 mol%) as a carbene precursor and NaO*t*Bu. After screening a variety of reaction conditions, it was found that the choice of *N*-substituent of the imidazolium salt proved to be the most important factor for this transformation (Table S1). The mesityl substituent on the NHC is crucial for the activity, while other imidazolium salts (IPr·HCl, INpEt·HCl) did not catalyze this transformation. Based on these results, we designed new unsymmetrical imidazolium ligands containing one mesityl substituent for the improvement of reaction efficiency. With the newly developed unsymmetrical NHC **A**, the corresponding product **3a** could be isolated in better yield (82%). Under the optimized reaction conditions, we have explored the substrate scope of this reaction (Scheme 2). A number of aryl halides **2** as well as diarylmethanes **1** smoothly underwent direct arylation of C(sp^3)–H bonds to afford the corresponding products **3a-3g** in good to excellent yields. With chiral NHC **A***, the reaction of **1a** with 4-bromotoluene (**2b**) which creates a new stereogenic center was then conducted. However, unfortunately, no enantioselectivity was observed, possibly due to the lack of chiral induction or racemization of the products.

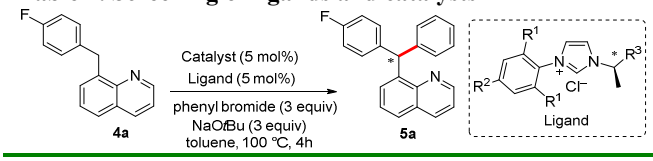
Scheme 2. Scope of 2-benzylpyridines and aryl bromides[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), $RhCl(PPh_3)_3$ (5 mol%), NHC **A** (5 mol%) and NaO*t*Bu (0.6 mmol) in toluene (0.5 mL) at 120°C under Ar, 12 h, isolated yield.

For the development of an asymmetric version, we envisioned that substrates that could make a more rigid metal complex would be more likely to give asymmetric induction. To test our hypothesis, 8-benzyl quinolines **4** were examined as substrates in which the nitrogen on quinoline could coordinate to the rhodium metal, resulting in a 5-membered metallacycle. To our delight, the desired product **5a** was obtained in 80% yield with 82:18 e.r. when the reaction of 8-(4-fluorobenzyl)quinoline (**4a**) and bromobenzene (**2a**) was carried out with chiral NHC **A*** (Table 1, entry 1). This result suggestthat the pre-coordination of substrates to the metal catalyst plays a significant role in asymmetric induction. Inspired by this result, a series of unsymmetrical chiral NHCs, which are accessible from readily available chiral amines and anilines in one step,[17] were further investigated (Table 1). It is noteworthy that an *o*-tolyl substituent (R^1=Me) on the NHC is critical for this transformation (Table S2), presumably to enable a cyclometalation of the benzylic position of the NHC which leads to a catalytically active species. Steric and electronic variations of R^3 did not improve either reactivity or enantioselectivity (entry 6-8). Further improvement of the e.r. was achieved with variation of R^2 without affecting the yields (entry 2-5). The 4-fluorophenyl substituent on R^2 proved to be the most effective one for this reaction, affording a yield of 90% with 87:13 e.r. (entry 4).Finally, prolonging the reaction time at a lower temperature (80°C) could slightly increase the e.r. while maintaining the yield (entry 8). We also explored other rhodium precursors by using NHC **A*** (entry 9-11). Both Rh(II) and Rh(III) precursors also gave product **5a** in similar yield but with lower enantioinduction (entry 10-11).

Table 1. Screening of ligands and catalysts[a]



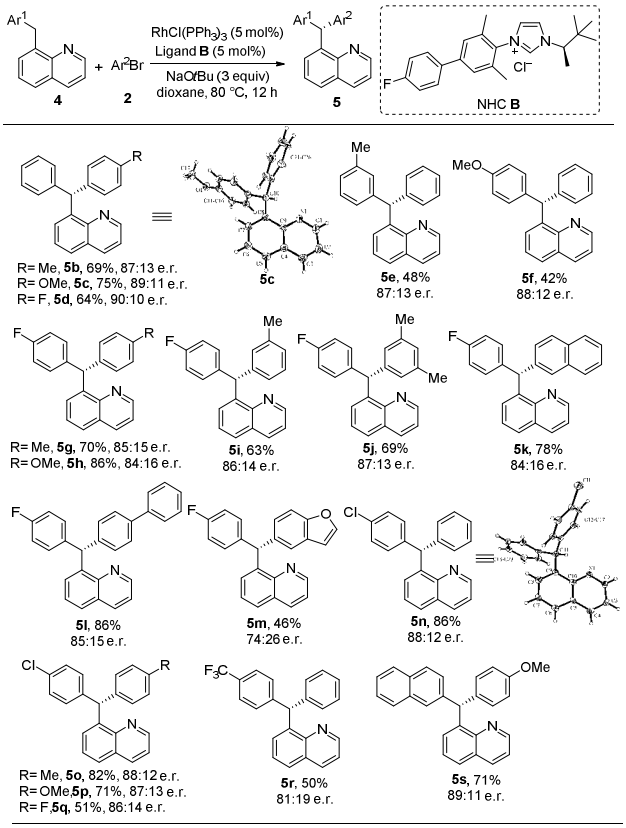
Entry	Catalyst	R^1	R^2	R^3	Yield (%)[b]	e.r[c]
1	$Rh(PPh_3)_3Cl$	Me	Me	*t*-Bu	80	82:18
2	$Rh(PPh_3)_3Cl$	Me	2-Np	*t*-Bu	90	87:13
3	$Rh(PPh_3)_3Cl$	Me	4-Py	*t*-Bu	43	86:14
4	$Rh(PPh_3)_3Cl$	Me	*p*-F C_6H_4	*t*-Bu	90	87:13
5[d]	$Rh(PPh_3)_3Cl$	Me	*p*-F C_6H_4	*t*-Bu	87 (85)[e]	89:11
6	$Rh(PPh_3)_3Cl$	Me	Me	cPr	27	55:45
7	$Rh(PPh_3)_3Cl$	Me	Me	Ad	82	81:19
8	$Rh(PPh_3)_3Cl$	Me	Me	Np	90	55:45
9[f]	$[Rh(cod)Cl]_2$	Me	Me	*t*-Bu	72	75:25
10[f]	$Rh_2(OAc)_2$	Me	Me	*t*-Bu	94	79:21
11[f]	$Rh(acac)_3$	Me	Me	*t*-Bu	41	78:22

[a]Reaction conditions: **4a** (0.1 mmol), phenylbromide (0.3 mmol), catalyst (5 mol%), NHC (5 mol%) and NaO*t*Bu (0.3 mmol) in toluene (0.25 mL) for 4 h at 100 °C under Ar. [b]GC-FID yield. [c]Determined by HPLC on a chiral stationary phase. [d]Reaction was carried out in 1,4-dioxane (0.25 mL) for 12 h at 80°C. [e]Isolated yield. [f]Reactions were performed with PCy_3 (10 mol%). Np=naphthyl, Py=pyrenyl, cPr=cyclopropyl, Ad=adamantyl.

Having established reaction conditions for the enantioselective C(sp^3)–H arylations of 8-(4-fluorobenzyl)quinoline (**4a**), we investigated the scope of the reaction (Scheme 3). We were pleased to observe that direct arylations of 8-benzyl quinoline (**4b**) with aryl bromides bearing both electron-donating groups (Me, OMe) and F in *para*- position were well-tolerated under the reaction conditions, and afforded the corresponding products **5b**–**5d** in good yields with good e.r. ranging from 87:13 to 90:10. Next, the influence of the electronic and steric nature of the substituents on the diarylmethanes was investigated with bromobenzene(**2a**). Electron-donating substituents in *meta*- and *para*- positions provided the corresponding products **5e** and **5f** in slightly lower yield but with similar e.r. On the other hand, the reactions of electron-poor substrates with a wide range of aryl bromides proceeded efficiently and afforded products **5g-5l** with better yield while maintaining the e.r. value. Notably, 5-bromobenzofurane is also competent, affording **5m**.[11b] Other electron-withdrawing groups (Cl, CF_3)-substituted substrates **4e**, **4f** as well as naphthyl-

substituted substrate **4g** were also tolerated, providing the corresponding products **5n-5s** in good yields with good e.r. The absolute configuration of **5c** and **5n** were determined by X-ray crystallographic analysis.[18] Recrystallization to enantiopurity was examined, with all selected samples isolated in excellent *ee* (**5c**, >99%; **5n**, >99%; **5p**, 95%) and moderate yields (see SI)**.**

Scheme 3. Scope of 8-benzyl quinolines and aryl bromides[a]



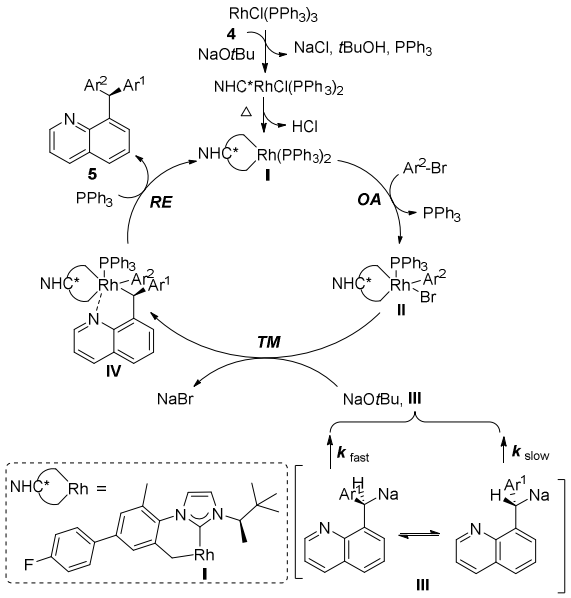
[a]Reaction conditions: **4** (0.2 mmol), **2** (0.6 mmol), $RhCl(PPh_3)_3$ (5 mol%), NHC **B** (5 mol%) and NaO*t*Bu (0.6 mmol) in 1,4-dioxane (0.5 mL) at 80 °C under argon for 12 h, isolated yield.

To gain insights into the reaction mechanism, we conducted a series of deuterium-incorporation experiments. When 3 equivalents of NaO*t*Bu was added to the substrate **4b** in a mixture of methanol-d_4 and 1,4-dioxane, 80% of deuterium was incorporated to the benzylic C(sp^3)–H bond of **4b** in the absence of catalyst and ligand. In contrast, no deuterium incorporation to the substrate was observed upon running the reaction with $Rh(PPh_3)_3Cl$ and NHC **B** in the absence of base. These results indicate that the reaction involves initial reversible deprotonation by the base. The isolated product **5a** was treated with the standard conditions. Despite basic conditions, no racemization of **5a** could be observed, retaining the same *ee*. The observation of relatively large KIE value (k_H/k_D = 2.77) from parallel reactions suggests that the rate determining step is probably the cleavage of C(sp^3)–H bond.

In order to gain structural information on the reactive species, we carried out a NMR study. When we mixed stoichiometric amounts of $RhCl(PPh_3)_3$, NHC **B** and NaO*t*Bu (3 equiv) in toluene-d_8, the ^{1}H NMR spectrum showed that one of the *ortho*-methyl C–H bonds on the aryl substituent of the NHC has been activated leading to a Rh–C bond, which renders the metal center highly electron rich presumably facilitating oxidative addition. In addition, this species may play a central role in chiral induction since the whole system is rigid, overcoming the possible rotation around the metal-carbon bond (**I**, Scheme 4).

To probe the order of events, ^{1}H, ^{19}F and ^{31}P NMR analyses of the stoichiometric reaction were conducted (see SI). The results showed that pre-formed rhodium complex does not interact with the substrate **4b**, while new signals appear readily even at room temperature in the presence of 4-bromoanisole **2c**. Therefore, we suggest that oxidative addition of arylbromide proceeded prior to transmetalation of **4** (Scheme 4).

Scheme 4. Proposed reaction mechanism



Recent papers report transition metal-free coupling reactions between haloarenes and arenes to form biaryls, triggered by alkali metal *tert*-butoxides with various additives.[19] These reactions are known to involve the generation of aryl radical intermediates, generated from potassium or sodium *tert*-butoxide. In a similar fashion, we considered that this reaction could proceed through a radical intermediate. Addition of neither BHT nor 1,1-diphenylethene to the reaction mixture decreased conversion to the desired product **5a**, suggesting that this reaction is not operating *via* a radical mechanism.

On the basis of above results and previous reports,[16,20] a plausible reaction mechanism is proposed in Scheme 4. The transformation is initiated by the coordination of in situ generated free NHC to the Rh metal complex, followed by intramolecular C–H bond activation of an aryl *ortho*-methyl on the carbene to produce reactive Rh(I)-complex **I**. Then, oxidative addition of aryl-halide into Rh-complex **I** is presumed to occur to give Rh(III)-complex **II** with concomitant loss of the associated ligands. Next, the deprotonated substrate **III,** which is generated by excess amount of NaO*t*Bu, undergoes transmetalation leading to Rh-complex **IV**. The transmetallation may be favored for one of the enantiomers **III**, possibly due to steric interactions. The desired product **5** is then produced by the reductive elimination of **IV**.

In summary, we have developed a novel Rh(I)/NHC catalytic system for site- and enantioselective direct arylations of C(sp^3)–H bonds. The reactions were applied for the synthesis of chiral triarylmethanes. Using $Rh(PPh_3)_3Cl$ and newly designed chiral NHCs, diverse triarylmethanes have been synthesized with good enantioselelctivities and yields. The mechanistic studies demonstrate that the newly developed NHC* undergoes an intramolecu-

lar C(sp^3)–H activation leading to a defined chiral environment without the necessity of a C_2 symmetric NHC. Further studies regarding the detailed reaction mechanism and explorations of the potential of newly developed chiral NHCs for other transformations are currently in progress.

ASSOCIATED CONTENT

Supporting Information.

Experimental procedure, characterization data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

glorius@uni-muenster.de

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REFERENCES

(1) For selected reviews, see: (a) Rouquet, G.; Chatani, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 11726-11743; (b) Li, H.; Li, B.-J.; Shi, Z.-J. *Catal. Sci. Technol.* **2011**, *1*, 191-206; (c) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem. Eur. J.* **2010**, *16*, 2654-2672.

(2) For selected papers of site-selective arylations, see: (a) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130,* 3266-3267; (b) Schipper, D. J.; Campeau, L.-C.; Fagnou, K. *Teterahedron* **2009**, *65*, 3155-3164; (c) Kwak, J.; Kim, M.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133,* 3780-3783.

(3) For selected papers, see: (a) Pedroni, J.; Cramer, N. *Angew. Chem. Int. Ed.* **2015**, *54*, 11826-11829; (b) Saget, T.; Cramer, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 12842-12845; (c) Saget, T.; Lemouzy, S. J.; Cramer, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 2238-2242; (d) Martin, N.; Pierre, C.; Davi, M.; Jazzar, R.; Baudoin, O. *Chem. Eur. J.* **2012**, *18*, 4480-4484; (e) Lee, T.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2016**, *55*, 8723-8727.

(4) For selected papers of Pd catalyzed reactions, see: (a) Zhang, F.-L.; Hong, K.; Li, T.-J.; Park, H.; Yu, J.-Q. *Science* **2016**, *351,* 252-256; (b) Chan, K. S. L.; Fu, H.-Y.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137,* 2042-2046; (c) Renaudat, A.; Jean-Gérard, L.; Jazzar, R.; Kefalidis, C. E.; Clot, E.; Baudoin, O. *Angew. Chem. Int. Ed.* **2010**, *49*, 7261-7265; For examples of Ir catalyzed reactions, see: (d) Tahara, Y.-K.; Michino, M.; Ito, M.; Kanyiva, K. S.; Shibata, T. *Chem. Commun.* **2015**, *51*, 16660-16663; (e) Pan, S.; Matsuo, Y.; Endo, K.; Shibata, T. *Tetrahedron* **2012**, *68*, 9009-9015.

(5) For selected papers and review, see: (a) Liao, K.; Negretti, S.; Musaev, D. G.; Bacsa, J.; Davies, H. M. L. *Nature* **2016**, *533*, 230-234; (b) Fu, L.; Guptill, D. M.; Davies, H. M. L. *J. Am. Chem. Soc.* **2016**, *138,* 5761-5764; (c) Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011**, 40 1857-1869; (d) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704-724.

(6) For the Pd-NHC catalyzed C(sp^3)–H functionalizations, see: (a) Ye, S.; Yang, W.; Coon, T.; Fanning, D.; Neubert, T.; Stamos, D.; Yu, J.-Q. *Chem. Eur. J.* **2016**, *22*, 4748-4752; (b) Hsiao, C.-C.; Lin, Y.-K.; Liu, C.-J.; Wu, T.-C.; Wu, Y.-T. *Adv. Synth. Catal.* **2010**, *352*, 3267-3274; For the Ni-NHC catalyzed C(sp^3)–H functionalization, see: (c) Fernández-Salas, J. A.; Marellia, E.; Nolan, S. P. *Chem. Sci.* **2015**, *6*, 4973-4977.

(7) For selected review, see: (a) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, *510*, 485-496; (b) Praetorius, J. M.; Crudden, C. M. *Dalton Trans* **2008**, 4079-4094.

(8) For the Pd/NHC*-catalyzed intramolecular asymmetric C(sp^3)–H arylations, see: (a) Nakanishi, M.; Katayev, D.; Besnard, C.; Kündig, E. P. *Angew. Chem. Int. Ed.* **2011**, *50*, 7438-7441; (b) Larionov, E.; Nakanishi, M.; Katayev, D.; Besnard, C.; Kündig, E. P. *Chem. Sci.* **2013**, *4*, 1995-2005.

(9) For selected reviews and papers, see: (a) Mondal, S.; Panda, G. *RSC Adv.* **2014**, *4*, 28317-28358; (b) Nair, V.; Thomas, S.; Mathew, S. C.; Abhilash, K. G. *Tetrahedron* **2006**, *62*, 6731-6747; (c) Parai, M. K.; Panda, G.; Chaturvedi, V.; Manju, Y. K.; Sinha, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 289-292.

(10) For recent papers, see: (a) Nambo, M.; Crudden, C. M. *ACS Catal.* **2015**, *5*, 4734-4742; (b) Nambo, M.; Ariki, Z. T.; Canseco-Gonzalez, D.; Beattie, D. D.; Crudden, C. M. *Org. Lett.* **2016**, *18*, 2339-2342.

(11) For selected papers, see: (a) Wood, P. M.; Woo, L. L.; Labrosse, J.-R.; Trusselle, M. N.; Abbate, S.; Longhi, G.; Castiglioni, E.; Lebon, F.; Purohit, A.; Reed, M. J. *J. Med. Chem.* **2008**, *51*, 4226-4238; (b) Asoh, K.; Kohchi, M.; Hyoudoh, I.; Ohtsuka, T.; Masubuchi, M.; Kawasaki, K.; Ebiike, H.; Shiratori, Y.; Fukami, T. A.; Kondoh, O.; Tsukaguchi, T.; Ishii, N.; Aoki, Y.; Shimma, N.; Sakaitani, M. *Bioorg. Med. Chem. Lett.* **2009**, *19,* 1753-1757; (c) Johnson, A. G.; Tranquilli, M. M.; Harris, M. R.; Jarvo, E. R. *Tetrahedron. Lett.* **2015**, *56*, 3486-3488. (12) For selected papers, see: (a) Taylor, B. L. H.; Harris, M. R.; Jarvo, E. R. *Angew. Chem. Int. Ed.* **2012**, *51*, 7790-7793; (b) Harris, M. R.; Hanna, L. E.; Greene, M. A.; Moore, C. E.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 3303-3306; (c) Matthew, S. C.; Glasspoole, B. W.; Eisenberger, P.; Crudden, C. M. *J. Am. Chem. Soc.* **2014**, *136*, 5828-5831.

(13) (a) Huang, Y.; Hayashi, T.; *J. Am. Chem. Soc.* **2015**, *137*, 7556-7559; (b) Liao, H.-H.; Chatupheeraphat, A.; Hsiao, C.-C.; Atodiresei, I.; Rueping, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 15540-15544; (c) Zhou, M.-H.; Jiang, Y.-J.; Fan, Y.-S.; Gao, Y.; Liu, S.; Zhang, S. *Org. Lett.* **2014**, *16*, 1096-1099; (d) Sun, F.-L., Zhang, X.-J.; Gu, Q.; He, Q.-L.; You, S.-L. *Eur. J. Org. Chem.* **2010**, 47-50; (e) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2008**, *47*, 4882-4886.

(14) Niwa, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 2373-2375.

(15) For selected papers, see: (a) Zhang, J.; Belloo, A.; Creamer, A. D.; Dreher, S. D.; Walsh, P. J. *J. Am. Chem. Soc.* **2012**, *134*, 13765-13772; (b) Zhang, J.; Bellomo, A.; Trongsiriwat, N.; Jia, T.; Carroll, P. J.; Dreher, S. D.; Tudge, M. T.; Yin, H.; Robinson, J. R.; Schelter, E. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2014**, *136*, 6276-6287.

(16) (a) Berman, A. M.; Lewis, J. C; Bergman, R. G.: Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 14926-14927; (b) Berman, A. M.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2010**, *75*, 7863-7868; For the example of *ortho*-alkylation: (c) Song, G.; Wylie. W. N. O, Hou, Z. *J. Am. Chem. Soc.* **2014**, *136,* 12209-12212.

(17) Queval, P.; Jahier, C.; Rouen, M.; Artur, I.; Legeay, J.-C.; Falivene, L.; Toupet, L.; Crévisy, C.; Cavallo, L.; Baslé, O.; Mauduit, M. *Angew. Chem. Int. Ed.* **2013**, 52, 14103-14107.

(18) CCDC 1498372 (**5c**) and CCDC 1487620 (**5n**) contain the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

(19) For selected papers, see: (a) Barham, J. P.; Coulthard, G.; Emery, K. J.; Doni, E.; Cumine, F.; Nocera, G.; John, M. P.; Berlouis, L. E. A.; McGuire, T.; Tuttle, T.; Murphy, J. A. *J. Am. Chem. Soc.* **2016**, *138*, 7402-7410; (b) Zhou, S.; Anderson, G. M.; Mondal, B.; Doni, E.; Ironmonger, V.; Kranz, M.; Tuttle, T.; Murphy, J. A. *Chem. Sci.* **2014**, *5*, 476-482; (c) Rueping, M.; Leiendecker, M.; Das, A.; Poisson, T.; Bui, L. *Chem. Commun.* **2011**, *47*, 10629-10631.

(20) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem. Int. Ed.* **2003**, *42*, 112-114.

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