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Fast Enantio- and Chemoselective Arylation of Ketones with Organoboronic Esters Enabled by Nickel/N-Heterocyclic Carbene Catalysis

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Dedicated to the 70th anniversary of Shanghai Institute of Organic Chemistry (SIOC)

Abstract: *A general, efficient, highly enantio- and chemoselective N-heterocyclic carbene (NHC)/Ni-catalyzed addition of readily available and stable arylboronic esters to ketones is reported. This protocol provides unexpectedly fast access (usually 10 min) to various chiral tertiary alcohols with exceptionally broad substrate scope and excellent functional group tolerance (76 examples, up to 98 % ee). This process is orthogonal to other known Ni-mediated Suzuki–Miyaura couplings, as it tolerates aryl chlorides, fluorides, ethers, esters, amides, nitriles, and alkyl chlorides. The reaction is applied to late-stage modifications of various densely functionalized medicinally relevant molecules. Preliminary mechanistic studies suggest that a rare enantioselective η^2-coordinating activation of ketone carbonyls is involved. This cross-coupling-like mechanism is expected to enable other challenging transformations of ketones.*

Optically active tertiary alcohols constitute an important class of structural units that are commonly found in pharmaceuticals, agrochemicals, and bioactive natural products (Figure 1 A).[1] Moreover, they serve as versatile building blocks for the synthesis of challenging targets, including all-carbon quaternary stereocenters.[2] Consequently, general methods to construct chiral tertiary alcohols have long been sought after in the chemical community.[3,4] Since the discovery of the Grignard reaction, the nucleophilic addition of organometallic reagents to ketones has been recognized as the most convenient method to synthesize achiral or chiral tertiary alcohols.[5,6] Although tremendous efforts have been devoted to carbonyl addition chemistry in the past century, several longstanding challenges remain (Figure 1 B). First, the use of highly basic and nucleophilic organometallic reagents, such as organomagnesium, organozinc, or organoaluminium, makes

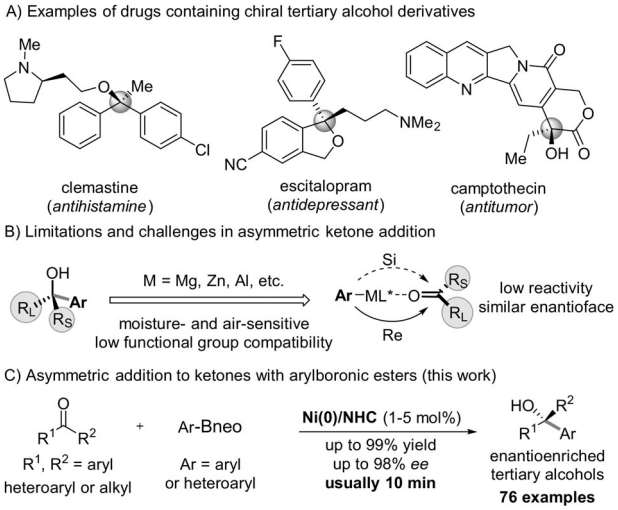

Figure 1. Construction of chiral tertiary alcohols via ketone additions.

the reactions less tolerant to functional groups. Moreover, the moisture- and air-sensitive nature of these organometallics further complicates their preparation and purification. As a result, these methods are usually not suitable for the direct transformation of highly functionalized compounds or late-stage functionalization of bioactive molecules.

In contrast, the wide availability and stability of organoboron nucleophiles have imparted exceptional functional group tolerance and great operational simplicity to the Suzuki–Miyaura couplings, making it one of the most frequently used reactions in organic chemistry.[7] In this context, we envisioned that an enantioselective addition method to ketones using arylboron nucleophiles instead of difficult-to-handle organometallics would greatly facilitate the preparation of chiral tertiary alcohols. However, in sharp contrast to aldehyde additions, the ketone addition generally suffers from low reactivities due to the increased steric hindrance and attenuated electrophilicity of the carbonyl group. Furthermore, the enantiofacial differentiation of ketones is more challenging.[3–5] Indeed, although there are various reports on asymmetric arylboration of aldehyde,[8] examples of analogous ketone addition are scarce and largely limited to electronically activated substrates[9] and intramolecular reactions,[10] or resulted in low enantioselectivity.[11] The single example of highly enantioselective catalytic arylboration of simple ketones has recently been reported by Deng, Tang, and co-workers, although the use of a noble

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metal (rhodium) catalyst, aryl ketones, and arylboroxines substrates is required.[12] Therefore, a general, practical, and enantioselective addition to simple ketones of arylboronic esters for the synthesis of chiral tertiary alcohols remains to be established.

We sought a chiral ligand for an earth-abundant metal catalyst to address the abovementioned longstanding unmet problems. We have recently developed a series of bulky C_2-symmetric chiral NHCs,[13] namely ANIPE- and SIPE-type ligands, and successfully applied them to asymmetric transition-metal catalysis.[14] We anticipate the presence of multiple C_2-symmetric chiral axes, as well as bulky and tunable N-substituents on the NHCs, would allow for high levels of enantiocontrol. Herein, we describe a general and highly enantioselective addition of arylboronic esters to simple ketones enabled by a Ni/NHC catalysis, providing exceptionally efficient and expedient access to a wide variety of chiral tertiary alcohols (Figure 1C). Importantly, this protocol is applicable to a series of highly functionalized drugs or intermediates derived from biologically relevant molecules.

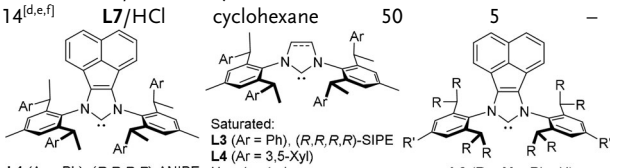
We started the studies by treating the model substrate 2-acetonaphthone (**1a**) with phenylboronic acid neopentylglycol ester (PhBneo, **2a**) in the presence of nickel catalyst and CsF. At first, a series of commonly used chiral phosphine and NHC ligands were tested and found to be ineffective for this arylation reaction (Supporting Information). However, the use of our ANIPE ligand (**L1**/HCl, Table 1, entry 1) gave promising results; the tertiary alcohol product **3a** was obtained in quantitative yield with 80% *ee*. The use of a bulkier ligand **L2** successfully delivered **3a** in improved enantioselectivity of 86% *ee* (entry 2). Saturated SIPE-type and unsaturated IPE-type ligands all decreased the enantioselectivity (entries 3–5). Compared to the arene solvent, ether and hydrocarbon solvent both afford slightly higher enantioselectivity (entries 6–7), and cyclohexane was chosen as the optimal solvent to give **3a** in 90% *ee*. Decreasing the reaction temperature to 50°C could maintain the reactivity and increase the enantioselectivity to 94% *ee* (entry 8). The use of bulkier phenylboronic acid pinacol ester (PhBpin) could give similar reaction outcomes (94% *ee*, entry 9). Importantly, we found that 2 mol% catalyst loading was enough to promote this reaction (entry 10). Further screening using MeONa as the base gave **3a** in quantitative yield with 95% *ee* (entry 11). To our surprise, this reaction was extremely fast and finished in 10 min at 50°C to afford the product in 98% isolated yield with 95% *ee* (entry 12). Interestingly, we found the use of a less bulky ligand (**L6**, with 2,6-diisopropylaniline fragments) and a more hindered ligand (**L7**, with 2,6-dibenzhydrylaniline fragments) both decreased the reactivity significantly (entries 13–14). As such, we concluded that the proper steric hindrance of ligands was critical for the arylation reaction to proceed fast.

With the optimized reaction conditions in hand, we next investigated the generality of ketone partners for this arylation reaction. As shown in Figure 2, a wide variety of commercially available ketones were applicable, furnishing chiral tertiary alcohols (**3a**–**4s**) in good to excellent yield and enantioselectivity (70–98% *ee*). The use of aryl methyl ketones delivered the corresponding products in outstanding

Table 1: Reaction optimization.

1a (0.2 mmol) **3a**

Entry	Ligand	Solvent	Temp. [°C]	Yield [%][a]	*ee* [%][b]
1	**L1**/HCl	toluene	80	99	80
2	**L2**/HCl	toluene	80	99	86
3	**L3**/HCl	toluene	80	99	67
4	**L4**/HCl	toluene	80	82	69
5	**L5**/HCl	toluene	80	98	67
6	**L2**/HCl	THF	80	99	88
7	**L2**/HCl	cyclohexane	80	99	90
8	**L2**/HCl	cyclohexane	50	99	94
9[c]	**L2**/HCl	cyclohexane	50	95	94
10[d]	**L2**/HCl	cyclohexane	50	99	94
11[d,e]	**L2**/HCl	cyclohexane	50	99	95
12[d,e,f]	**L2**/HCl	cyclohexane	50	99(98)	95
13[d,e,f]	**L6**/HCl	cyclohexane	50	54	–
14[d,e,f]	**L7**/HCl	cyclohexane	50	5	–



[a] Determined by GC using crude samples, isolated yield shown in parentheses. [b] Determined by HPLC analysis with a chiral stationary phase. [c] PhBPin was used. [d] 2 mol% catalyst loading. [e] Using MeONa instead of CsF. [f] 10 min.

enantioselectivity (**3a**–**3q**, 91–97% *ee*). Both electron-rich and electron-deficient aromatic ketones with *para*-, *meta*-, or *ortho*-substitutions served as suitable substrates. Moreover, substrates bearing medicinally important heterocycles, such as a morpholine (**3e**), a benzofuran (**3r**), a benzothiophene (**3s**), furans (**3u**, **3v**), a thiophene (**3x**), a pyridine (**3w**), an indole (**3t**), a thiazole (**3z**), a carbazole (**3y**), and a quinoline (**4a**), were all compatible. Chiral heterocyclic tertiary alcohols (**3r**–**4a**) were obtained in good to high yield with remarkable enantiocontrol (93–97% *ee*). In addition to acyclic substrates, the use of cyclic ketones with different ring sizes (**4b**–**4d**) and heteroaromatic cyclic ketones (**4e**–**4h**) all afforded products in exceptional enantioselectivity (94–98% *ee*). For alkyl aryl ketones with small differences of two substituents on the prochiral carbon center, good to excellent enantioselectivity could still be obtained (**4i**–**4o**). In the case of benzoylpropionate, lactonization product (**4o**) was obtained from the corresponding tertiary alcohol in a single operation. Interestingly, the use of dialkyl ketones, whose enantiofaces are challenging to discriminate and can readily undergo enolization, also furnished products with synthetically useful outcomes (**4p**–**4s**). It bears mentioning that most reactions were conducted in 10 min, with several exceptions due to the low solubility or large steric hindrance of substrates. Notably, many functional groups, including ethers (**3b**, **3e**, **3k**), a trifluoromethoxyl (**3f**), trifluoromethyl groups (**3g**, **3l**), an ester (**3h**), a nitrile (**3i**), a sulfuryl (**3j**), a ferrocenyl (**3p**), an

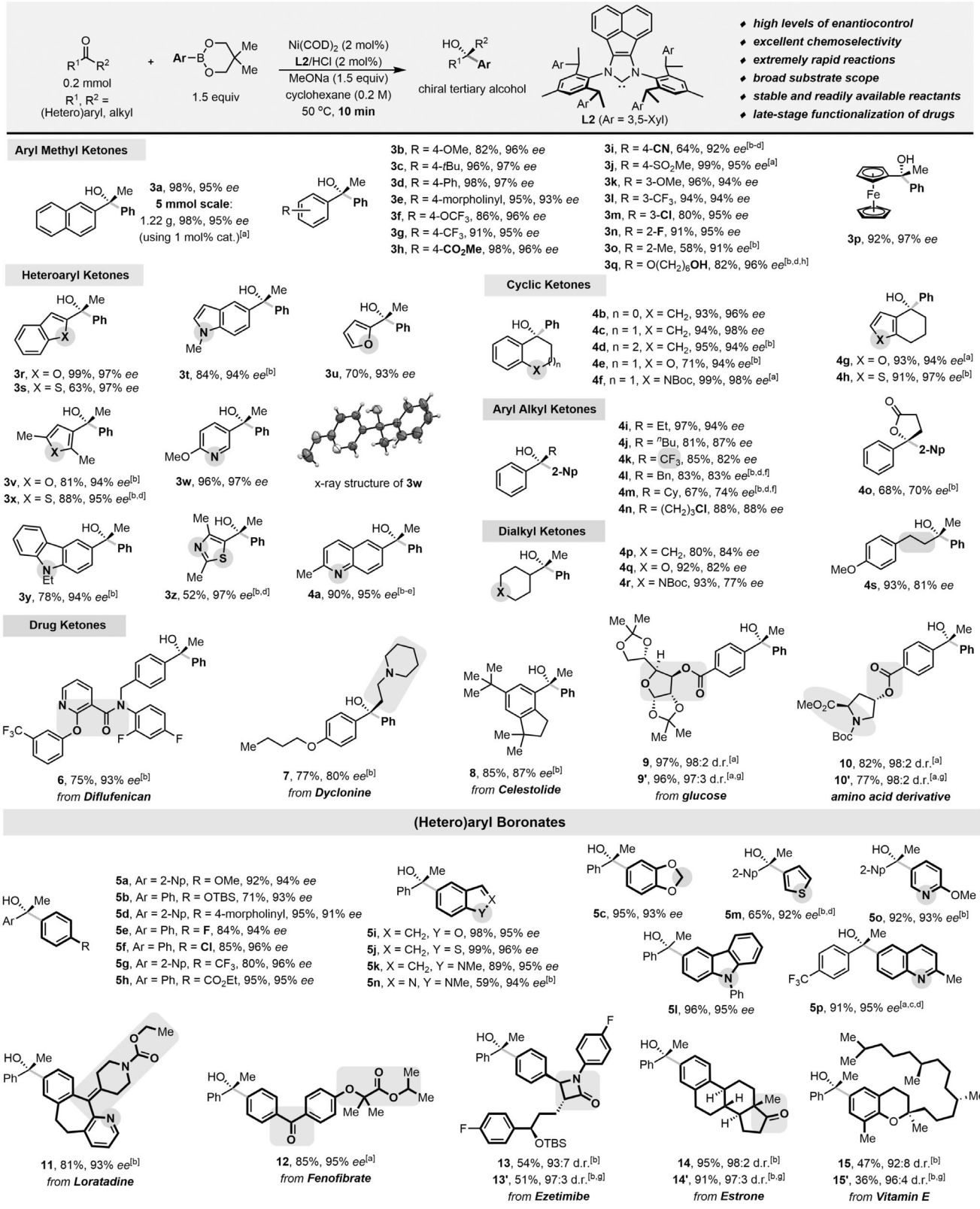


Figure 2. Substrate scope. Isolated yields are shown; *ee* and d.r. values were determined by chiral HPLC analysis; 2-naphthyl (2-Np). [a] 1 h; [b] 24 h; [c] 80 °C; [d] using 5 mol% catalyst; [e] toluene as the solvent; [f] **L1**/HCl was used; [g] using *ent*-**L2**/HCl; [h] using 3.0 equiv of PhBneo.

unprotected alcohol (**3q**), an alkyl chloride (**4n**), an aryl chloride(**3m**) and fluoride (**3n**), could be well tolerated. The absolute stereochemistry of **3w** was determined by X-ray crystallography. Finally, we successfully performed a gram-

scale reaction (5-mmol scale, **3a**) while simultaneously lowering the catalyst loading to 1 mol%. The alcohol product was obtained in undiminished yield and enantioselectivity, highlighting the practicality of this method.

Subsequently, we explored the scope of organoboron coupling partners. As shown in Figure 2, we found that both electron-rich and electron-poor arylboronic esters (**5a**–**h**), as well as heteroaryl boronic esters (**5i**–**p**), smoothly undergo arylation to give products in high yield and enantioselectivity (91–96% *ee*, **5a**–**p**). Organoboron and ketone substrates that possess many sensitive functional groups to nickel catalysts were all well- tolerated. For example, the competitive Ni-catalyzed Suzuki reactions of various well-developed electrophiles,[15] including aryl chlorides, fluorides, ethers, esters, nitriles, amides, alkyl chlorides, as well as the undesired reactivity of benzylic alcohol derivatives, were smoothly avoided under the current reaction conditions, providing excellent opportunities for further elaborations.

The excellent functional group compatibility of this protocol and the wide occurrence of ketone groups encouraged us to expand the scope of this arylation method. The applicability of new methodologies to the late-stage modification of complex natural products or highly functionalized synthetic intermediates is a highly desirable feature, as analogs of bioactive molecules can be prepared without laborious de novo synthesis. Accordingly, substrates derived from diflufenican (**6**, an herbicide), dyclonine (**7**, a local anesthetic), and celestolide (**8**, a spice) were subjected to our arylation conditions and were all successfully arylated to give products with high yield and enantioselectivity (80–93% *ee*). Complex carbohydrate and amino acid derivatives were also applied to this arylation protocol, providing products (**9**–**10**) in high yields with excellent, catalyst-controlled diastereoselectivity (97:3–98:2 d.r.). Moreover, asymmetric arylation reactions using arylboronates derived from pharmaceuticals, such as fenofibrate (**11**) and ezetimibe (**12**), two widely prescribed drugs for the treatment of hyperlipidemia, loratadine (**13**, an antiallergic medication), estrone (**14**, a hormone), and δ-vitamin E (**15**, an antioxidant), were successfully performed. Highly functionalized chiral tertiary alcohols were generated in excellent enantioselectivity (93–95% *ee*) or catalyst-controlled diastereoselectivity (92:8–98:2 d.r.). Interestingly, aryl methyl ketones could be selectively arylated in the presence of diaryl ketone (**12**) and bulky dialkyl ketone (**14**), probably due to steric reasons.

Next, we conducted preliminary mechanistic studies to probe the plausible mechanism. We prepared complex **16** by simply mixing NHC/Ni^0 complex and ketones (Figure 3A). Complex **16** with a 14e configuration was unstable. The addition of secondary ligands like PCy_3 or a pyridine-containing ketone could stabilize oxanickelacycle to give **17** or **18** bearing a 16e configuration. The ^{13}C NMR chemical shifts for **16**–**18** (78.2, 77.9, 73.2 ppm) are shifted dramatically upfield compared with that of corresponding ketone substrates. The structure of **18**, a dimer, was unambiguously confirmed by X-ray crystal diffraction. These observations would suggest the η^2-coordinating activation of ketone and the subsequent oxidative cyclization step.[16] We then treated **16** with PhBneo in the absence of base at 50 °C for two hours;

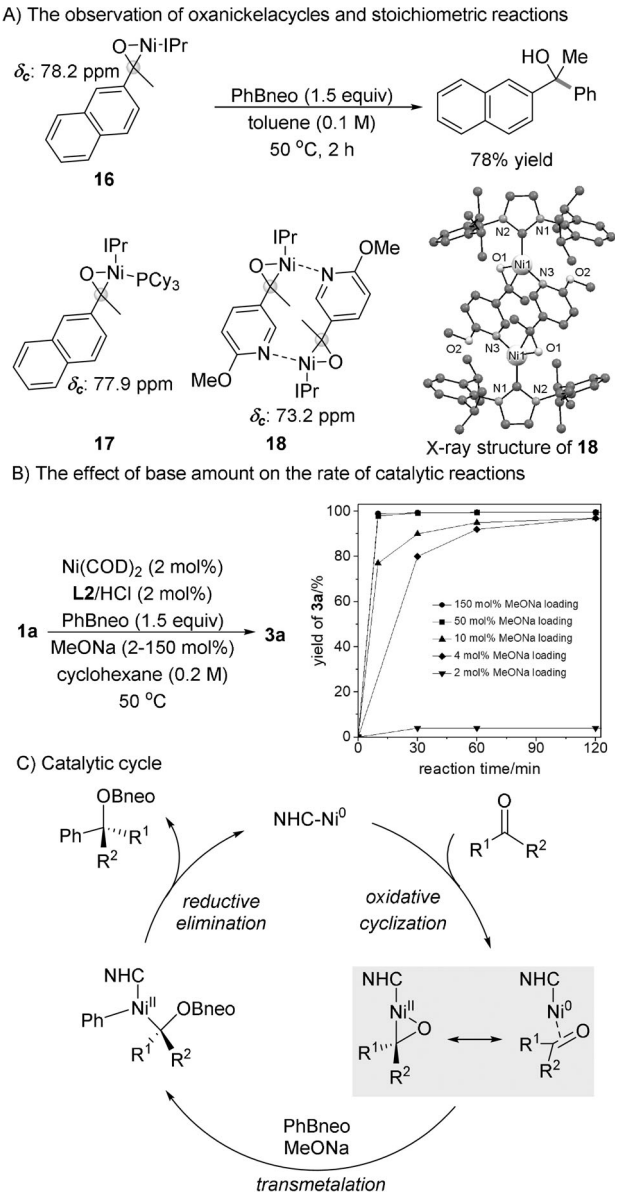


Figure 3. Proposed mechanism.

alcohol product was obtained in 78% yield. Remarkably, we found the addition of MeONa accelerates the catalytic reaction, which might promote the transmetalation step (Figure 3B). While almost no conversions were observed in the absence of excess base (2 mol% of base used for the in situ generations of the Ni/NHC catalyst), the use of 0.5 equiv or more MeONa finished the reaction in 10 min. Based on our observations and previous reports from the groups of Ogoshi, Itami, and others,[16,17] we proposed a catalytic cycle shown in Figure 3C. An electron-donating NHC chelated Ni^0 species facilitates the η^2-activation of ketone carbonyls and oxidative cyclization to afford an oxanickelacycle. A subsequent base-promoted transmetalation forms an aryl-alkyl nickel complex, which undergoes reductive elimination to give alcohol product and Ni^0 catalyst for the next catalytic cycle.

In conclusion, we have developed a general, efficient, highly enantio- and chemoselective NHC/Ni-catalyzed aryl-

boration of ketones. The key to the fast reaction and excellent enantiocontrol is the employment of a bulky C_2-symmetric chiral NHC ligand for Ni catalyst. This process tolerates an exceptionally broad scope of functional groups and heterocycles, providing various chiral tertiary alcohols from readily available and stable reactants. Beyond the immediate synthetic utility, we anticipate that this rare enantioselective η^2-coordinating activation of ketone would inspire further development of other challenging yet important asymmetric transformations of ketones.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: arylboronic esters · chiral NHC ligands · chiral tertiary alcohols · nickel catalysis

[1] For books, see: a) *Quaternary stereocenters, challenges and solutions for organic synthesis* (Eds.: J. Christoffers, A. Baro), Wiley-VCH, Weinheim, **2005**; b) *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**.

[2] a) L. Chen, X.-P. Yin, C.-H. Wang, J. Zhou, *Org. Biomol. Chem.* **2014**, *12*, 6033 – 6048; b) Q. Zhou, K. M. Cobb, T. Tan, M. P. Watson, *J. Am. Chem. Soc.* **2016**, *138*, 12057 – 12060.

[3] For selected reviews, see: a) M. Shibasaki, M. Kanai, *Chem. Rev.* **2008**, *108*, 2853 – 2873; b) O. Riant, J. Hannedouche, *Org. Biomol. Chem.* **2007**, *5*, 873 – 888; c) D. Leonori, V. K. Aggarwal, *Acc. Chem. Res.* **2014**, *47*, 3174 – 3183; d) Y.-L. Liu, X.-T. Lin, *Adv. Synth. Catal.* **2019**, *361*, 876 – 918.

[4] For selected examples, see: a) J. L. Stymiest, V. Bagutski, R. M. French, V. K. Aggarwal, *Nature* **2008**, *456*, 778 – 782; b) K. C. Harper, M. S. Sigman, *Science* **2011**, *333*, 1875 – 1878; c) Y. Yang, I. B. Perry, G. Lu, P. Liu, S. L. Buchwald, *Science* **2016**, *353*, 144 – 150; d) S.-L. Shi, L.-W. Xu, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 6638 – 6639.

[5] a) R. Noyori, M. Kitamura, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49 – 69; *Angew. Chem.* **1991**, *103*, 34 – 55; b) L. Pu, H.-B. Yu, *Chem. Rev.* **2001**, *101*, 757 – 824; c) M. Hatano, K. Ishihara, *Synthesis* **2008**, 1647 – 1675; d) J. F. Collados, R. Solà, S. R. Harutyunyan, B. Maciá, *ACS Catal.* **2016**, *6*, 1952 – 1970.

[6] For selected enantioselective examples of organometallic addition to ketones, see: **Zn**: a) P. I. Dosa, G. C. Fu, *J. Am. Chem. Soc.* **1998**, *120*, 445 – 446; b) D. J. Ramón, M. Yus, *Angew. Chem. Int. Ed.* **2004**, *43*, 284 – 287; *Angew. Chem.* **2004**, *116*, 286 – 289; c) H. Li, C. Garcia, P. J. Walsh, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5425 – 5427; **Al**: d) C.-A. Chen, K.-H. Wu, H.-M. Gau, *Angew. Chem. Int. Ed.* **2007**, *46*, 5373 – 5376; *Angew. Chem.* **2007**, *119*, 5469 – 5472; **Ti**: e) K.-H. Wu, Y.-Y. Kuo, C.-A. Chen, Y.-L. Huang, H.-M. Gau, *Adv. Synth. Catal.* **2013**, *355*, 1001 – 1008; **Mg**: f) E. Fernández-Mateos, B. Maciá, M. Yus, *Eur. J. Org. Chem.* **2014**, 6519 – 6526.

[7] A. Suzuki, *Angew. Chem. Int. Ed.* **2011**, *50*, 6722 – 6737; *Angew. Chem.* **2011**, *123*, 6854 – 6869.

[8] For selected examples on metal-catalyzed asymmetric arylboration of aldehyde, see: **Rh:** a) M. Sakai, M. Ueda, N. Miyaura, *Angew. Chem. Int. Ed.* **1998**, *37*, 3279 – 3281; *Angew. Chem.* **1998**, *110*, 3475 – 3477; b) H.-F. Duan, J.-H. Xie, W.-J. Shi, Q. Zhang, Q.-L. Zhou, *Org. Lett.* **2006**, *8*, 1479 – 1481; c) T. Nishimura, H. Kumamoto, M. Nagaosa, T. Hayashi, *Chem. Commun.* **2009**, 5713 – 5715; **Ru:** d) Y. Yamamoto, K. Kurihara, N. Miyaura, *Angew. Chem. Int. Ed.* **2009**, *48*, 4414 – 4416; *Angew. Chem.* **2009**, *121*, 4478 – 4480; **Cu:** e) D. Tomita, M. Kanai, M. Shibasaki, *Chem. Asian J.* **2006**, *1*, 161 – 166; **Ni:** f) T. Arao, K. Kondo, T. Aoyama, *Tetrahedron Lett.* **2007**, *48*, 4115 – 4117; **Co:** g) J. Karthikeyan, M. Jeganmohan, C.-H. Cheng, *Chem. Eur. J.* **2010**, *16*, 8989 – 8992; For amino- or iminoalcohol-catalyzed asymmetric aldehyde arylation via boron-to-zinc transmetalation, see: h) C. Bolm, J. Rudolph, *J. Am. Chem. Soc.* **2002**, *124*, 14850 – 14851.

[9] For additions to α-keto esters, see: a) H.-F. Duan, J.-H. Xie, X.-C. Qiao, L.-X. Wang, Q.-L. Zhou, *Angew. Chem. Int. Ed.* **2008**, *47*, 4351 – 4353; *Angew. Chem.* **2008**, *120*, 4423 – 4425; b) F. Cai, X. Pu, X. Qi, V. Lynch, A. Radha, J. M. Ready, *J. Am. Chem. Soc.* **2011**, *133*, 18066 – 18069; c) Y. Yamamoto, T. Shirai, M. Watanabe, K. Kurihara, N. Miyaura, *Molecules* **2011**, *16*, 5020 – 5034; d) T.-S. Zhu, S.-S. Jin, M.-H. Xu, *Angew. Chem. Int. Ed.* **2012**, *51*, 780 – 783; *Angew. Chem.* **2012**, *124*, 804 – 807; For additions to trifluoromethyl ketones, see: e) S. L. X. Martina, R. B. C. Jagt, J. G. de Vries, B. L. Feringa, A. J. Minnaard, *Chem. Commun.* **2006**, 4093 – 4095; f) R. Li, K. Luo, Y. Hu, W. Tang, *Adv. Synth. Catal.* **2013**, *355*, 1297 – 1302; For additions to isatins, see: g) R. Shintani, M. Inoue, T. Hayashi, *Angew. Chem. Int. Ed.* **2006**, *45*, 3353 – 3356; *Angew. Chem.* **2006**, *118*, 3431 – 3434; h) Z. Liu, P. Gu, M. Shi, P. McDowell, G. Li, *Org. Lett.* **2011**, *13*, 2314 – 2317.

[10] Intramolecular additions: a) G. Liu, X. Lu, *J. Am. Chem. Soc.* **2006**, *128*, 16504 – 16505; b) G. Liu, X. Lu, *Tetrahedron* **2008**, *64*, 7324 – 7330; c) D. Tomita, K. Yamatsugu, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 6946 – 6948; d) R. Sarpong, G. L. Gallego, *Chem. Sci.* **2012**, *3*, 1338 – 1342; e) D. W. Low, G. Pattison, M. D. Wieczysty, G. H. Churchill, H. W. Lam, *Org. Lett.* **2012**, *14*, 2548 – 2551; f) D.-X. Zhu, W.-W. Chen, M.-H. Xu, *Tetrahedron* **2016**, *72*, 2637 – 2642; g) C. Ni, J. Gao, X. Fang, *Chem. Commun.* **2020**, *56*, 2654 – 2657.

[11] a) J. Bouffard, K. Itami, *Org. Lett.* **2009**, *11*, 4410 – 4413; b) Y.-X. Liao, C.-H. Xing, Q.-S. Hu, *Org. Lett.* **2012**, *14*, 1544 – 1547; c) T. Korenaga, A. Ko, K. Uotani, Y. Tanaka, T. Sakai, *Angew. Chem. Int. Ed.* **2011**, *50*, 10703 – 10707; *Angew. Chem.* **2011**, *123*, 10891 – 10895.

[12] L. Huang, J. Zhu, G. Jiao, Z. Wang, X. Yu, W.-P. Deng, W. Tang, *Angew. Chem. Int. Ed.* **2016**, *55*, 4527 – 4531; *Angew. Chem.* **2016**, *128*, 4603 – 4607.

[13] a) D. Janssen-Müller, C. Schlepphorst, F. Glorius, *Chem. Soc. Rev.* **2017**, *46*, 4845 – 4854; b) F. Wang, L.-J. Liu, W. Wang, S. Li, M. Shi, *Coord. Chem. Rev.* **2012**, *256*, 804 – 853.

[14] a) Y. Cai, X.-T. Yang, S.-Q. Zhang, F. Li, Y.-Q. Li, L.-X. Ruan, X. Hong, S.-L. Shi, *Angew. Chem. Int. Ed.* **2018**, *57*, 1376 – 1380; *Angew. Chem.* **2018**, *130*, 1390 – 1394; b) Y. Cai, J.-W. Zhang, F. Li, J.-M. Liu, S.-L. Shi, *ACS Catal.* **2019**, *9*, 1 – 6; c) W.-B. Zhang, X.-T. Yang, J.-B. Ma, Z.-M. Su, S.-L. Shi, *J. Am. Chem. Soc.* **2019**, *141*, 5628 – 5634; d) D. Shen, Y. Xu, S.-L. Shi, *J. Am. Chem. Soc.* **2019**, *141*, 14938 – 14945; e) Y. Cai, X. Ye, S. Liu, S.-L. Shi, *Angew. Chem. Int. Ed.* **2019**, *58*, 13433 – 13437; *Angew. Chem.* **2019**, *131*, 13567 – 13571; f) D. Shen, W.-B. Zhang, Z. Li, S.-L. Shi, Y. Xu, *Adv. Synth. Catal.* **2020**, *362*, 1125 – 1130; For a concomitant development of ligands, see: g) J. Diesel, A. M. Finogenova, N. Cramer, *J. Am. Chem. Soc.* **2018**, *140*, 4489 – 4493; h) J. Diesel, D. Grosheva, S. Kodama, N. Cramer, *Angew.*

Chem. Int. Ed. **2019**, *58*, 11044 – 11048; *Angew. Chem.* **2019**, *131*, 11160 – 11164.
[15] F.-S. Han, *Chem. Soc. Rev.* **2013**, *42*, 5270 – 5298.
[16] a) Y. Hoshimoto, M. Ohashi, S. Ogoshi, *Acc. Chem. Res.* **2015**, *48*, 1746 – 1755; b) J. Montgomery, *Angew. Chem. Int. Ed.* **2004**, *43*, 3890 – 3908; *Angew. Chem.* **2004**, *116*, 3980 – 3998; c) E. A. Standley, S. Z. Tasker, K. L. Jensen, T. F. Jamison, *Acc. Chem. Res.* **2015**, *48*, 1503 – 1514.
[17] a) R. Kumar, Y. Hoshimoto, H. Yabuki, M. Ohashi, S. Ogoshi, *J. Am. Chem. Soc.* **2015**, *137*, 11838 – 11845; b) K. Hirano, H. Yorimitsu, K. Oshima, *Org. Lett.* **2005**, *7*, 4689 – 4691; c) C. Lei, Y. J. Yip, J. S. Zhou, *J. Am. Chem. Soc.* **2017**, *139*, 6086 – 6089; d) D. K. Nielsen, A. G. Doyle, *Angew. Chem. Int. Ed.* **2011**, *50*, 6056 – 6059; *Angew. Chem.* **2011**, *123*, 6180 – 6183. Also, see refs. [11a], [8f].

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Communications

Arylation Reactions

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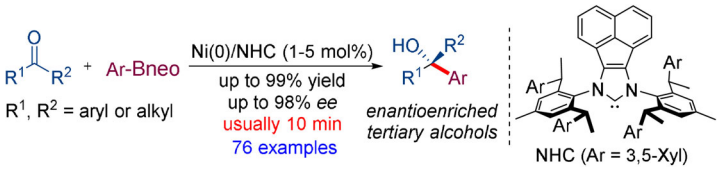
Fast Enantio- and Chemoselective Arylation of Ketones with Organoboronic Esters Enabled by Nickel/N-Heterocyclic Carbene Catalysis



A method for general asymmetric addition of arylborons to simple ketones is reported, which is enabled by nickel/N-heterocyclic carbene catalysis. Chiral tertiary alcohols are furnished with high efficiency and excellent levels of enantio- and chemocontrol, and the method offers a broad substrate scope.