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## Accepted Article

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VERY IMPORTANT PUBLICATION

FULL PAPER

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# Direct and Efficient C(sp$^3$)-H Bond Alkylation of Tetrahydroisoquinolines and Isochroman with Alkylzinc Reagents

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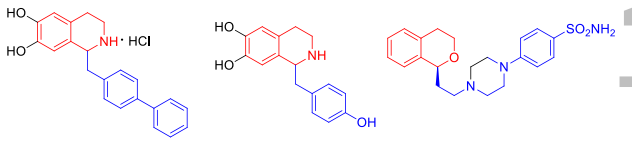
**Abstract.** An efficient C(sp$^3$)–H bond alkylation of tetrahydroisoquinolines and isochroman with alkylzinc reagents was demonstrated. This transformation could be readily performed under mild conditions in the absence of a heavy metal catalyst, affording a wide range of potentially biologically active compounds. In addition, this approach exhibited excellent compatibility with various sensitive functional groups such as a cyano group, an ester group as well as a boronic acid pinacol ester group.

**Keywords:** C–H functionalization; alkylation; tetrahydroisoquinoline; zinc reagents; catalyst-free

## Introduction

During the past two decades, C−H functionalization has been extensively developed and widely used in organic and medicinal chemistry.[1] However, in contrast with better developed C−H arylation reactions, the alkylation of C(sp$^3$)−H bonds constitutes a fundamental challenge in organic synthesis.[2] Especially, efforts to couple C(sp$^3$)–H bonds with organometallic reagents have generally been far less successful.[3]

Heterocycles are ubiquitous structural motifs in many facets of chemical science and can be readily found in natural products, materials, crop protection and pharmaceutical industries. Amongst various heterocycles, tetrahydroisoquinolines (THIQs) and isochromans have recently received much attention because they exhibit a wide variety of biological activities.[4] For instance, 1-biphenyl-4-ylmethyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrochloride (compound **A**, Figure 1) has cytotoxic activity in human gliomas and other diverse human cancers.[5] Higenamine (compound **B**, Figure 1), having a history of use in traditional medicine, is a $\beta_2$ adrenoreceptor agonist.[6] In addition, compound **C** (Sonepiprazole, Figure 1) was found to be a potent $D_4$ antagonist.[7]




compound **A** (1-biphenyl-4-ylmethyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrochloride) compound **B** (Higenamine) compound **C** (Sonepiprazole)

**Figure 1.** Selected biologically active 1-alkylated tetraisoquinolines and isochromanes.

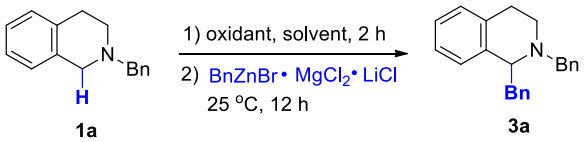
Driven by the pre-mentioned prevalence, enormous endeavors were devoted to the synthesis of these bioactive compounds. The recent use of high efficiency, and step economy C–H activation methods represents an ideal strategy in the synthesis of heterocycles. Since cross-dehydrogenative coupling (CDC) reactions[8] emerged as a concisely synthetic method to construct C(sp$^3$)−C(sp$^3$) bonds, a range of methods for the synthesis of 1-alkylated THIQs and isochromans through CDC reactions have been studied.[9] However, these CDC reactions normally required a heavy metal catalyst and harsh reaction conditions, which largely limited the utility in organic synthesis. An attractive alternative approach for the construction of 1-alkylated THIQs and isochromans involves the coupling of C(sp$^3$)–H bonds with organometallic reagents under oxidative conditions.

Recently, alkyl magnesium reagents[10] and alkyl boron reagents[11] were successfully applied to the transition-metal-free alkylation of THIQs and benzopyrans respectively. Although the transition-metal-catalyst free C($sp^3$)–H bond arylation of tetrahydroisoquinoline (THIQ) derivatives and isochromans with arylzinc reagents have been achieved,[12] the alkylation of THIQ derivatives with organozinc reagents still required the addition of $CuCl_2$.[13] In other words, the transition-metal-catalyst free C-H alkylation of tetraisoquinolines and isochromans with alkylzinc reagents which exhibit better compatibility with sensitive functional groups remains undeveloped. In view of the synthetic utility and certain limitations of existing methods in particular regarding substrate scope, herein, we describe a convenient, transition-metal-catalyst free, and broadly applicable oxidative cross-coupling reaction of tetraisoquinolines and isochromans with alkylzinc reagents to access diverse 1-alkylated tetraisoquinoline and isochroman derivatives in an effective manner.

## Results and Discussion

We began to explore the alkylation of THIQs and isochromans with alkylzinc reagents coordinated with $MgCl_2$ and LiCl, which displayed better reactivity because of the presence of $MgCl_2$ and LiCl.[12, 14] When the oxidation of **1a** by using 2,3-dicyano-5,6-dichlorobenzoquinone (DDQ), (diacetoxyiodo)benzene (PIDA), diethyl azodicarboxylate (DEAD), or [bis(trifluoroacetoxy)iodo]benzene (PIFA) as an oxidant was conducted in 2-MeTHF or THF at room temperature, only trace of coupling product **3a** were obtained or no desired product was observed (Table 1, entries 1-5). Delightedly, the oxidation of 2-benzyl-1,2,3,4-tetrahydroisoquinoline to an iminium cation could be achieved by using PIFA as an organic oxidant in 1,2-dichloroethane (DCE) at 80 °C within 2 h. The subsequent treatment of the intermediate ion with BnZnBr·$MgCl_2$·LiCl, which was prepared by the insertion of magnesium turnings into benzyl bromide in the presence of $ZnCl_2$ and LiCl,[14] afforded the desired product **3a** in the yield of 63% (Table 1, entry 6). Use of 1.5 equivalents of BnZnBr·$MgCl_2$·LiCl decreased slightly the yield of **3a** to 51% (Table 1, entry 7), and the increase in the amounts of BnZnBr·$MgCl_2$·LiCl to 4 equivalents didn't improve the yield (Table 1, entry 8). In the absence of the oxidant, no desired product was observed (Table 1, entry 9).

**Table 1.** Optimization of reaction conditions[a)]




| Entry | Oxidant | Solvent | Oxidation temperature | Yield of **3a**[b)] |
|---|---|---|---|---|
| 1 | DDQ | 2-MeTHF | 25 °C | trace |
| 2 | PIDA | 2-MeTHF | 25 °C | 0 |
| 3 | DEAD | THF | 25 °C | 0 |
| 4 | DEAD, PIFA[c)] | THF | 25 °C | 0 |
| 5 | PIFA | 2-MeTHF | 25 °C | trace |
| 6 | PIFA | DCE | 80 °C | 63% |
| 7[d)] | PIFA | DCE | 80 °C | 51% |
| 8[e)] | PIFA | DCE | 80 °C | 62% |
| 9 | | DCE | 80 °C | 0 |

[a)]General conditions: after the mixture of **1a** (0.5 mmol) and oxidant (1.1 equiv) was stirred for 2 h in solvent (2.5 mL) at 25 °C to 80 °C, benzylzinc reagent (1.5 mmol) was added, and the reaction mixture was stirred for 12 h at 25 °C. [b)]Isolated yield. [c)]The oxidation of **1a** (0.5 mmol) with DEAD (20 mol%) and PIFA (1.1 equiv) was conducted at 25 °C within 5 h. [d)]1.5 Equivalents of BnZnBr·$MgCl_2$·LiCl was used. [e)]4 Equivalents of BnZnBr·$MgCl_2$·LiCl was used.

Next, we proceeded to examine the reaction compatibility of alkylzinc reagents with 2-benzyl-1,2,3,4-tetrahydroisoquinoline under oxidative conditions (Table 2). Under similar conditions, the oxidative cross-coupling of alkylzinc reagents bearing a methoxy group with *N*-benzyl-THIQ gave the corresponding product **3b** in 81% yield. Benzylzinc reagents substituted with electron-withdrawing groups could also react with *N*-benzyl-THIQ, giving the desired products **3c-f** in 41-72% yields. In addition, propargylzinc reagent gave the desired product **3g**. The reaction could also be readily expanded to other alkylzinc reagents demonstrating the generality of this process. The oxidation of 2-benzyl-1,2,3,4-tetrahydroisoquinoline (0.5 mmol) with PIFA (1.1 equiv) in DCE (2.5 mL) at 80 °C within 2 h, and subsequent treatment with *n*-butylzinc reagent prepared by the insertion of magnesium into 1-bromobutane in the presence of $ZnCl_2$ and LiCl afforded the coupling product **3h** in the yield of 59%. Notably, secondary alkylation of C($sp^3$)–H bond with cyclohexylzinc reagent could also be accomplished, although steric hindrance at the α position (see **3i**) may result in a slight decrease of the reaction yield under the similar conditions.

**Table 2.** Reaction scope with different alkylzinc reagents.[a, b)]

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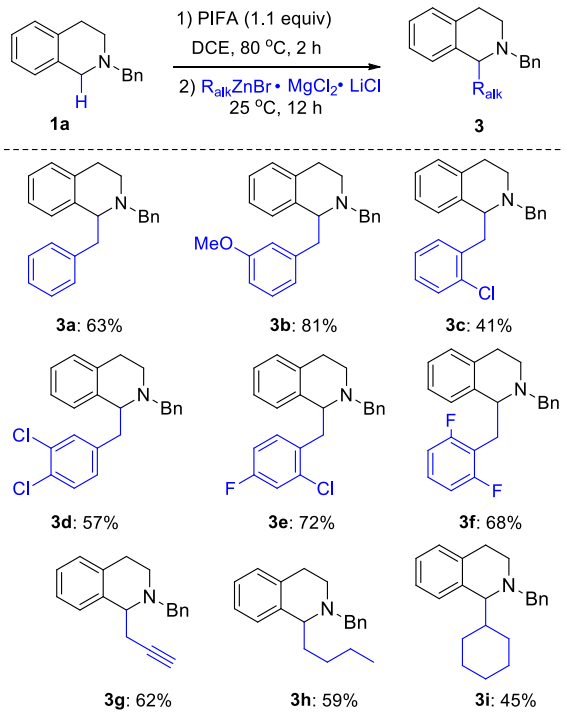
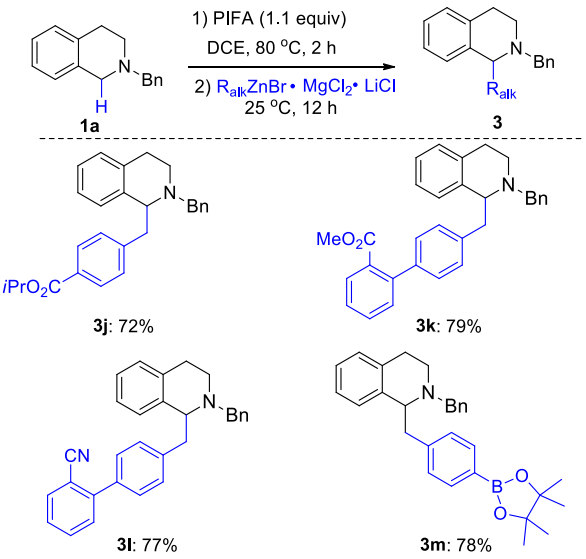



[a)]The reaction was performed by the oxidation of **1a** (0.5 mmol) and PIFA (1.1 equiv) in DCE (2.5 mL) at 80 °C for 2 h and subsequent treatment with organozinc reagent (1.5 mmol) at 25 °C for 12 h. [b)]Isolated yield.

Remarkably, the oxidative alkylation of THIQs with alkylzinc reagents showed excellent compatibility with various sensitive functional groups. As shown in Table 3, under similar conditions, benzylzinc reagents bearing an ester group smoothly underwent C($sp^3$)–H bond alkylation with *N*-benzyl-THIQ. The oxidation of *N*-benzyl-THIQ using PIFA was carried out in DCE within 2 h at 80 °C, and subsequent reactions with (4-(isopropoxycarbonyl)benzyl)zinc reagent and ((2'-(methoxycarbonyl)-[1,1'-biphenyl]-4-yl)methyl)zinc reagent at room temperature afforded the corresponding products **3j-k** in 72-79% yields respectively. Interestingly, alkylzinc reagent containing a cyano group reacted well with *N*-benzyl-THIQ, affording the expected product **3l** in 77% yield. Under identical conditions, the reaction of alkylzinc reagent bearing a boronic acid pinacol ester group with *N*-benzyl-THIQ provided the corresponding coupled product **3m** in the yield of 78%.

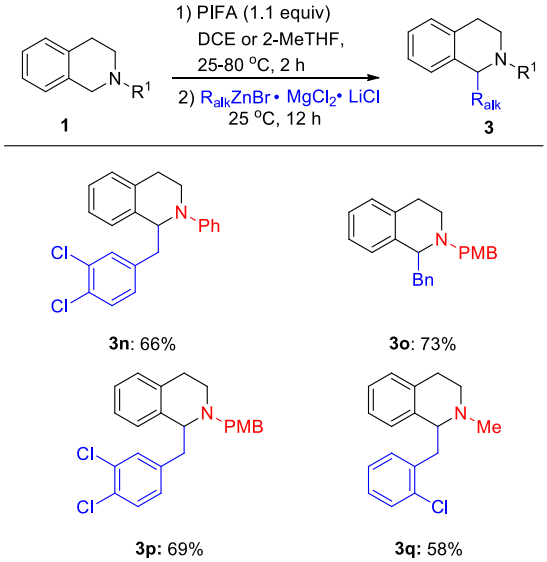
**Table 3.** Reaction scope with alkylzinc reagents bearing sensitive functional groups.[a, b)]




[a)]The reaction was performed by the oxidation of **1a** (0.5 mmol) and PIFA (1.1 equiv) in DCE (2.5 mL) at 80 °C for 2 h and subsequent treatment with organozinc reagent (1.5 mmol) at **25 °C** for 12 h. [b)]Isolated yield.

As shown in Table 4, the effect of *N*-substituents in THIQs on the conversion of the reaction was studied. Besides benzyl protecting groups, the coupling of THIQs with nitrogen bearing a phenyl group or benzyl substituents with strong electron-donating groups like a methoxy group also carried out well under mild conditions, furnishing the expected products **3n-p** in good yields. Interestingly, a useful yield (see **3q**) was obtained for *N*-methyl-THIQ whose reaction with arylzinc reagents was not observed. Unfortunately, under the optimum conditions, 2-phenylisoindoline and N-Boc-protected THIQ as substrates did not react with alkylzinc reagents.

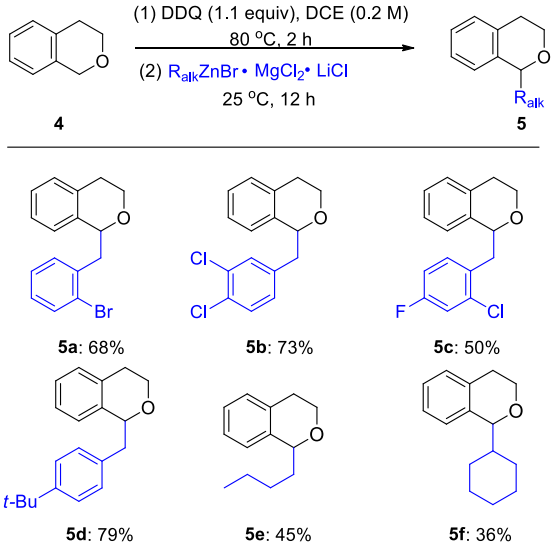
**Table 4.** C($sp^3$)–H Bond alkylation of THIQ derivatives. [a, b)]



[a]The reaction was performed by the oxidation of **1** (0.5 mmol) and PIFA (1.1 equiv) in DCE (2.5 mL) or 2-MeTHF (2.5 mL) at 25-80 °C for 2 h and subsequent treatment with organozinc reagent (1.5 mmol) at **25 °C** for 12 h. [b]Isolated yield.

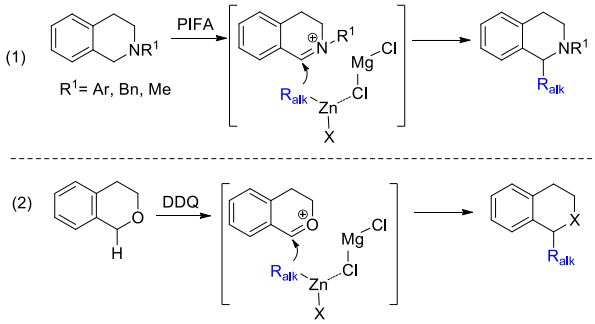
Normally, the reaction of the corresponding less reactive C($sp^3$)–H bonds next to an oxygen atom with less reactive organozinc reagents is nontrivial. Surprisingly, the substrate scope of the transition-metal-catalyst free C-H alkylation could be expanded to isochroman (Table 5). The oxidation of isochroman (1 mmol) with 2,3-dicyano-5,6-dichlorobenzoquinone (DDQ, 1.1 equiv) in DCE (5 mL) at 80 °C within 2 h,[12b] and subsequent treatment with 2-bromobenzylzinc reagent prepared by the insertion of magnesium into 1-bromo-2-(bromomethyl)benzene in the presence of $ZnCl_2$ and LiCl afforded the coupling product **5a** in the yield of 68%. The example **5a** was noteworthy, since the presence of bromide reserved a platform for the further products manupulation. In a similar manner, isochroman reacted successfully with various benzylzinc reagents bearing electron-withdrawing groups or electron-donating groups, furnishing the corresponding products **5b-d** in 50-79% yields. In addition, the coupling of isochroman with unbranched *n*-butylzinc reagent and secondary alkylzinc reagent provided the expected products **5e** and **5f** respectively.

**Table 5.** C($sp^3$)–H Bond alkylation of isochroman. [a, b]



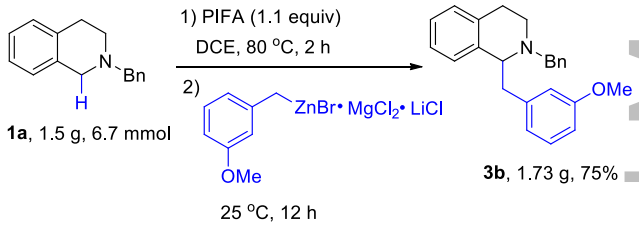

[a]The reaction was performed by the oxidation of **4** (1 mmol) and DDQ (1.1 equiv) in DCE (5 mL) at 80 °C for 2 h and subsequent treatment with organozinc reagent (1.5 mmol) at 25 °C for 12 h. [b]Isolated yield.

A plausible reaction mechanism for the C($sp^3$)-H alkylation of THIQs and isochroman with alkylzinc reagents is shown in Scheme 1. A radical cation generated by a single electron transfer from THIQs or isochroman to oxidant is accessed through H-atom abstraction to form a cation.[15] The subsequent addition of reactive alkylzinc reagents to ions affords the desired coupling products.




**Scheme 1.** Proposed mechanism for the C-H bond alkylation of THIQs and isochroman with alkylzinc reagents.

Finally, the gram-scale C-H bond alkylation of THIQs and isochroman with alkylzinc reagents was explored using substrate **1a** and 3-methoxybenzylzinc reagent. To our gratification, 1.5 g of 2-benzyl-1,2,3,4-tetrahydroisoquinoline successfully afforded a satisfactory 75% isolated yield of desired product **3b** (Scheme 2). This result renders this protocol potentially useful in industry.




**Scheme 2.** Gram-scale C-H bond alkylation of THIQ with alkylzinc reagent.

## Conclusion

In summary, we have developed a novel C($sp^3$)–H bond alkylation of THIQs and isochroman with alkylzinc reagents in the absence of a transition-metal catalyst. The convenient, practical and environmentally benign process could tolerate a wide range of functionalities, and showed facile accessibility to potentially biologically active compounds. Further studies on the scope, and applications of this reaction are now under investigation.

## Experimental Section

**General procedure for the reaction of tetrahydroisoquinolines with alkylzinc reagents:** A dry 25-mL sealed tube was evacuated and purged

with nitrogen gas three times. To the mixture of [bis(trifluoroacetoxy)iodo]benzene (PIFA) (1.1 equiv) and 1,2-dichloroethane (0.2 M) was added tetrahydroisoquinolines (1 equiv) under nitrogen atmosphere. The reaction mixture was stirred for 2 h at 80 °C. The mixture was allowed to cool to room temperature, and the corresponding alkylzinc reagent (3 equiv) was added dropwise at room temperature. After stirring for 12 h, water (20 mL) were then added to the reaction mixture. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine and dried over magnesium sulfate. The solvent was removed by rotary evaporation and purification by flash column chromatography on silica gel using petroleum ether/ethyl acetate as an eluent gave the expected products.

**General procedure for the reaction of isochroman with alkylzinc reagents:** A dry 25-mL sealed tube was evacuated and purged with nitrogen gas three times. To the mixture of DDQ (1.1 equiv) and 1,2-dichloroethane (0.2 M) was added isochroman (1 equiv) under nitrogen atmosphere. The reaction mixture was stirred for 2 h at 80 °C. The mixture was allowed to cool to room temperature, and the corresponding alkylzinc reagent (3 equiv) was added dropwise at room temperature. After stirring for 12 h, water (20 mL) were then added to the reaction mixture. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine and dried over magnesium sulfate. The solvent was removed by rotary evaporation and purification by flash column chromatography on silica gel using petroleum ether/ethyl acetate as an eluent gave the expected products.

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## References

[1] For selected reviews and references, see: a) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169. b) J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740–4761. c) D. A. Colby, A. S. Tsai, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2012**, *45*, 814–825. d) S. De Sarkar, W. Liu, S. I. Kozhushkov, L. Ackermann, *Adv. Synth. Catal.* **2014**, *356*, 1461–1479. e) O. Daugulis, J. Roane, L. D. Tran, *Acc. Chem. Res.* **2015**, *48*, 1053–1064. f) Z. Peng, Z. Yu, T. Li, N. Li, Y. Wang, L. Song, C. Jiang, *Organometallics* **2017**, *36*, 2826–2831.

[2] For selected reviews and references, see: a) B.-J. Li, Z.-J. Shi, *Chem. Soc. Rev.* **2012**, *41*, 5588–5598. b) L. Ackermann, *Chem. Commun.* **2010**, *46*, 4866–4877. c) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed*. **2009**, *48*, 5094–5115. d) D. A. Colby, A. S. Tsai, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res*. **2012**, *45*, 814–825. e) D.-H. Wang, M. Wasa, R. Giri, J.-Q. Yu, *J. Am. Chem. Soc*. **2008**, *130*, 7190–7191. f) A. J. Young, M. S. White, *J. Am. Chem. Soc*. **2008**, *130*, 14090–14091. g) D. Shabashov, O. Daugulis, *J. Am. Chem. Soc*. **2010**, *132*, 3965–3972. h) S.-Y. Zhang, G. He, W. A. Nack, Y.-S. Zhao, L. Qiong, G. Chen, *J. Am. Chem. Soc*. **2013**, 135, 2124–2127. i) S.-Y. Zhang, Q. Li, G. He, W. A. Nack, G. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 12135–12141. j) B. Wang, X. Wu, R. Jiao, S.-Y. Zhang, W. A. Nack, G. He, G. Chen, *Org. Chem. Front.* **2015**, *2*, 1318–1321.

[3] For selected reviews, see: a) M. Wasa, K. M. Engle, J.-Q. Yu, *Isr. J. Chem.* **2010**, *50*, 605–616. b) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Commun.***2010**, *46*, 677–685.

[4] a) S. Yamaori, M. Kushihara, I. Yamamoto, K. Watanabe, *Biochem. Pharmacol*. **2010**, *79*, 1691–1698. b) U. Albrecht, M. Lalk, P. Langer, *Bioorg. Med. Chem.* **2005**, *13*, 1531–1536. c) D. Ameen, T. J. Snape, *Med. Chem. Commun*. **2013**, *4*6, 893–907. d) Z.-Y. Lu, Z.-J. Lin, W.-L. Wang, L. Du, T.-J. Zhu, Y.-C. Fang, Q.-Q. Gu, W.-M. Zhu, *J. Nat. Prod*. **2008**, *71*, 543–546. e) M. J. de Groot, A. A. Alex, B. C. Jones, *J. Med. Chem*. **2002**, *45*, 1983–1993. f) B. R. Clark, R. J. Capon, E. Lacey, S. Tennant, J. H. Gill, *Org. Biomol. Chem*. **2006**, *4*, 1520−1528. g) H.-C. Liu, L. Du, T.-J. Zhu, D.-H. Li, M. Y. Geng, Q.-Q. Gu, *Helv. Chim. Acta* **2010**, *93*, 2224−2230. h) R. Silvestri, M. Artico, G. De Martino, R. Ragno, S. Massa, R. Loddo, C. Murgioni, A. G. Loi, P. La Colla, A. Pani, *J. Med. Chem*. **2002**, *45*, 1567−1576. i) P. S. Charifson, *Drugs Future* **1989**, *14*, 1179–1185. j) B. Hoffman, S. J. Cho, W. Zheng, S. Wyrick, D. E. Nichols, R. B. Mailman, A. Tropsha, *J. Med. Chem*. **1999**, *42*, 3217–3226. k) M. Chrzanowska, A. Grajewska, M. D. Rozwadowska, *Chem. Rev*. **2016**, *116*, 12369–12465. l) J. D. Scott, R. M. Williams, *Chem. Rev*. **2002**, *102*, 1669–1730.

[5] M. L. Mohler, G.-S. Kang, S.-S. Hong, R. Patil, O. V. Kirichenko, W. Li, I. M. Rakov, E. E. Geisert, D. D. Miller, *J. Med. Chem*. **2006**, *49*, 5845–5848.

[6] Y. Kashiwada, A. Aoshima, Y. Ikeshiro, Y.-P. Chen, H. Furukawa, M. Itoigawa, T. Fujioka, K. Mihashi, L. M. Cosentino, S. L. Morris-Natschke, K.-H. Lee, *Bioorg. Med. Chem.* **2005**, *13*, 443–448.

[7] R. E. TenBrink, C. L. Bergh, J. N. Duncan, D. W. Harris, R. M. Huff, R. A. Lahti, C. F. Lawson, B. S. Lutzke, I. J. Martin, S. A. Rees, S. K. Schlachter, J. C. Sih, M.W. Smith, *J. Med. Chem*. **1996**, *39*, 2435–2437.

[8] For selected reviews, see: a) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215–1292. b) S. A. Girard, T. Knauber, C.-J. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 74–100. c) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335–344. d) J. L. Roizen, M. E. Harvey, J. Du Bois, *Acc. Chem. Res.* **2012**, *45*, 911–922. e) B. V. Varun, J. Dhineshkumar,

K. R. Bettadapur, Y. Siddaraju, K. Alagiri, K. R. Prabhu, *Tetrahedron Lett.* **2017**, *58*, 803–824.

[9] For selected references, see: a) Y. Zhang, C.-J. Li, *J. Am. Chem. Soc.* **2006**, *128*, 4242–4243. b) Y. Zhang, C.-J. Li, *Angew. Chem. Int. Ed.* **2006**, *45*, 1949–1952. c) M. Ghobrial, K. Harhammer, M. D. Mihovilovic, M. Schnürch, *Chem. Commun.* **2010**, *46*, 8836−8838. d) X. Liu, B. Sun, Z. Xie, X. Qin, L. Liu, H. Lou, *J. Org. Chem.* **2013**, *78*, 3104–3112. e) X. Pan, Q. Hu, W. Chen, X. Liu, B. Sun, Z. Huang, Z. Zeng, L. Wang, D. Zhao, M. Ji, L. Liu, H. Lou, *Tetrahedron* **2014**, *70*, 3447–3451. f) J. Feng, M.-F. Lv, G.-P. Lu, C. Cai, *Org. Chem. Front.* **2015**, *2*, 60–64. g) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 3672–3673.

[10] a) W. Muramatsu, K. Nakano, C.-J. Li, *Org. Biomol. Chem.* **2014**, *12*, 2189–2192. b) W. Muramatsu, K. Nakano, C.-J. Li, *Org. Lett.* **2013**, *15*, 3650–3653. c) W. Muramatsu, K. Nakano, *Org. Lett.* **2014**, *16*, 2042–2045. d) W. Muramatsu, K. Nakano, *Org. Lett.* **2015**, *17*, 1549–1552. e) K. N. Singh, S. V. Kessar, P. Singh, P. Singh, M. Kaur, A. Batra, *Synthesis* **2014**, *46*, 2644–2650. f) W. Muramatsu, K. Nakano, *Tetrahedron Lett.* **2015**, *56*, 437–440. g) G. Oss, S. D. de Vos, K. N. H. Luc, J. B. Harper, T. V. Nguyen, *J. Org. Chem.* **2018**, *83*, 1000–1010.

[11] W. Chen, Z. Xie, H. Zheng, H. Lou, L. Liu, *Org. Lett.* **2014**, *16*, 5988–5991.

[12] a) Z. Peng, Z. Yu, D.-H. Chen, S. Liang, L. Zhang, D. Zhao, L. Song, C. Jiang, *Synlett* **2017**, *28*: 1835-1839. b) Z. Peng, Y. Wang, Z. Yu, D. Zhao, L. Song, C. Jiang, *J. Org. Chem.* **2018**, *83*, 7900–7906.

[13] T. Wang, M. Schrempp, A. Berndhäuser, O. Schiemann, D. Menche, *Org. Lett.* **2015**, *17*, 3982–3985.

[14] A. Metzger, S. Bernhardt, G. Manolikakes, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 4665–4668.

[15] a) A. S.-K. Tsang, P. Jensen, J. M. Hook, A. S. K. Hashmi, M. H. Todd, *Pure Appl. Chem.* 2011, *83*, 655–665. b) H. H. Jung, P. E. Floreancig, *Tetrahedron* 2009, *65*, 10830–10836.

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**FULL PAPER**

# Direct and Efficient C($sp^3$)-H Bond Alkylation of Tetrahydroisoquinolines and Isochroman with Alkylzinc Reagents

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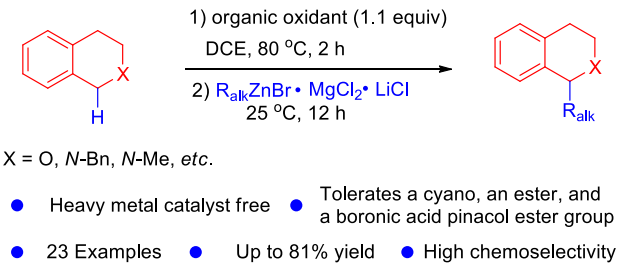


X = O, *N*-Bn, *N*-Me, *etc*.

- Heavy metal catalyst free
- Tolerates a cyano, an ester, and a boronic acid pinacol ester group
- 23 Examples
- Up to 81% yield
- High chemoselectivity