Organic LETTERS

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# Nickel-Catalyzed Reductive Methylation of Alkyl Halides and Acid Chlorides with Methyl *p*-Tosylate

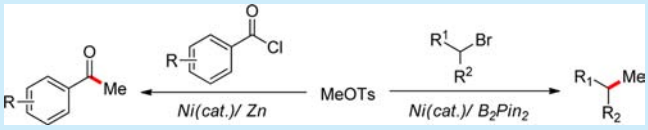
Zhuye Liang,[†,§] Weichao Xue,[‡,§] Kunhua Lin,*[,‡] and Hegui Gong*[,‡]

[†]College of Chemistry and Molecular Engineering, Zhengzhou University, 100 Science Road, Zhengzhou 450001, China

[‡]Department of Chemistry, Shanghai University, 99 Shang-Da Road, Shanghai 200444, China

Supporting Information

**ABSTRACT:** Methylation of unactivated alkyl halides and acid chlorides under Ni-catalyzed reductive coupling conditions led to efficient formation of methylated alkanes and ketones using methyl *p*-methyl tosylate as the methylation reagent. Moderate to excellent coupling yields as well as excellent functional group tolerance were observed under the present mild and easy-to-operate reaction conditions.



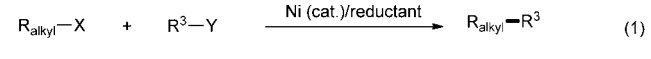

Methyl groups are the smallest carbon substituents that play important roles in many medicinal compounds such as in the top-selling drug Seretide[1] and in materials such as poly(methyl methacrylate) and poly(propylene oxide)s.[2] In addition to the conventional coupling of methyl halides with alkyl or aryl metallic reagents,[3] methylation on aryl and alkyl carbons can also be realized via transition-metal-catalyzed coupling of Me-metallic nucleophiles with organoelectrophiles.[4−6] Therein, the methyl and more hindered alkyl nucleophiles generally illustrate similar reactivities in the C−C bond-forming process. For instance, Jarvo reported that methylation of chiral benzylic ethers led to asymmetric production of benzylic methanes, which can be extended to more sterically bulky alkyl groups.[5] Another notable protocol to benzyl-Me compounds disclosed by Shi emphasizes the reaction of benzyl alcohol with Me.[6] Recently, methylation of aryl carbons can also be accessed through aryl C−H bond activation protocols.[7] Methylation via C−H activation of $sp^3$ carbons is also disclosed; however, it was often a constraint to directing group-assisted Pd-catalyzed methods.[8]

In light of the recent development of nickel-catalyzed reductive coupling of alkyl electrophiles with other electrophiles that have been disclosed by us and others,[9−13] we reasoned that direct coupling of methyl electrophiles with other organo halides would provide a more straightforward means to methylated products. Interestingly, methylation of other electrophiles with methyl electrophiles under the well-developed reductive coupling conditions has not been revealed (Scheme 1, eq 1). This is possibly due to rapid dimerization or hydrodehalogenation of the most accessible methyl electrophile source, e.g., MeI. Indeed, investigation of the coupling of MeI with aryl, allyl, and alkyl electrophiles proved to be ineffective under the Ni-catalyzed, zinc-mediated reductive coupling conditions that have been developed from our laboratory for unactivated alkyl halides.[9]

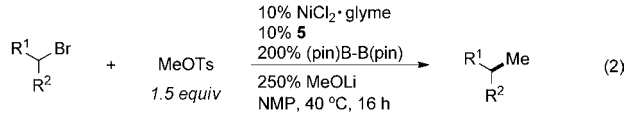
Previously, we have developed an efficient cross-coupling of two unactivated alkyl halides by employing bis(pinacolato)-diboron as the terminal reductant, in which only 1.5 equiv of primary bromides was employed for coupling with secondary bromides.[14] Meanwhile, we examined the coupling of 4-bromo-1-tosylpiperidine (**1**) with *n*-heptyl tosylate, which delivered the desired product in a low yield.[14] The formation of a $C(sp^3)$−$C(sp^3)$ bond using primary alkyl tosylate suggests that it might be possible to develop an efficient method for methylation of alkyl halides with methyl tosylate, wherein the distinctive reactivity of methyl tosylate may allow the nickel catalyst to effectively bias the two coupling partners. Herein, we describe the achievement of this objective, specifically, nickel-catalyzed coupling of methyl *p*-toluenesulfonate with alkyl bromides, that occurs under very mild conditions as shown in eq 2 (Scheme 1). In addition, reductive alkylation of acid chlorides with MeOTs was also investigated and proved to be effective.

**Scheme 1. Ni-catalyzed Reductive Coupling of Alkyl Halides with Methyl *p*-Tosylate**

*Previous work:* methylation not successful




*This work:*

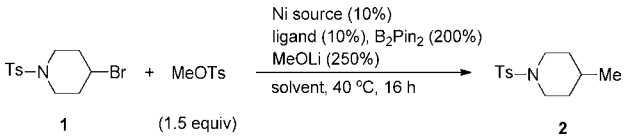



At the outset, the reaction conditions for Ni-catalyzed reductive coupling of two alkyl electrophiles (alkyl ≠ Me) was tested for the coupling of MeOTs with **1**.[14] The desired product **2** was obtained in a trace amount (Table 1, entry 1). However, under similar conditions using $NiCl_2$·glyme as the precatalyst, compound **2** was obtained in 56% yield (entry 2). Use of 2 equiv of MeOTs resulted in a lower yield (entry 3). Further

**Received:** September 11, 2014
**Published:** October 21, 2014

   dx.doi.org/10.1021/ol502682q | *Org. Lett.* 2014, 16, 5620−5623

**Table 1. Optimization for the Coupling of 1 and MeOTs**




1 (1.5 equiv) 2

| entry[a] | catalyst | ligand | solvent | yield[b] (%) |
|---|---|---|---|---|
| 1 | $NiI_2$ | **3a** | NMP | 6 |
| 2 | $NiCl_2$·glyme | **3a** | NMP | 56 |
| 3 | $NiCl_2$·glyme | **3a** | NMP | 47[c] |
| 4 | $NiCl_2$·glyme | **3b** | NMP | 55 |
| 5 | $NiCl_2$·glyme | **3c** | NMP | 55 |
| 6 | $NiCl_2$·glyme | **3d** | NMP | 49 |
| 7 | $NiCl_2$·glyme | **4** | NMP | 21 |
| 8 | $NiCl_2$·glyme | **5** | NMP | 65 |
| 9 | $NiCl_2$·glyme | **6** | NMP | 33 |
| 10 | $NiCl_2$·glyme | **7** | NMP | 7 |
| 11 | $NiBr_2$·diglyme | **5** | NMP | 68 |
| 12 | $Ni(COD)_2$ | **5** | NMP | 65 |
| 13 | $NiCl_2$·glyme | **5** | NMP/$iPr_2O$ = 7:3 | 85 |
| 14 | $NiCl_2$·glyme | **5** | DMA/$iPr_2O$ = 7:3 | 71 |
| 15 | $NiCl_2$·glyme | **5** | NMP/MeCN = 7:3 | 80 |

[a]Reaction conditions: **1** (100 mol %, 0.15 M in NMP), MeOTs (150 mol %), $NiCl_2$·glyme (10 mol %), $B_2(Pin)_2$ (200 mol %), ligand (10 mol %), MeOLi (250 mol %), NMP (1 mL). [b]Yields were determined by using GC–MS with 1-tosylpyrrolidine as an internal standard (calibrated). [c]2.0 equiv of MeOTs.

examination of the ligands, e.g., **3b–d** and **4–7**, indicated **5** (Figure 1) to be optimal (entries 4–10), generating **2** in 65%

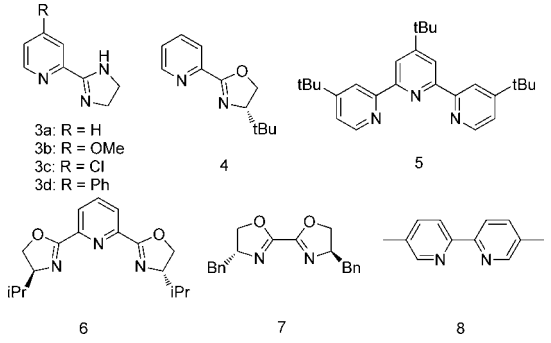
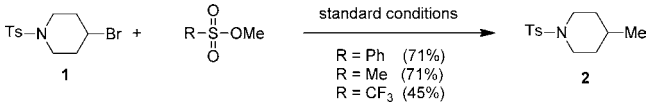



**Figure 1.** Structures of ligands.

yield (entry 8). With ligand **5**, other Ni sources were generally inferior, except $Ni(COD)_2$ and $NiBr_2$·diglyme which gave **2** with comparable results (entries 11 and 12). Finally, extensive examination of solvents showed that a mixture of NMP/$iPr_2O$ in a ratio of 7:3 is optimal (entries 13–15), which gave rise to **2** in a best 85% yield (entry 13). Under the optimized conditions for **1**, the iodo analogue, 4-iodo-1-tosylpiperidine, was less effective and only resulted in **2** in 64% yield. The employment of MeI in place of MeOTs led to a trace amount of product. Under the optimized reaction conditions, coupling of **1** with other sulfonates such as methyl phenylsulfonate, methyl methylsulfonate, and methyl trifluorosulfonate was inferior to MeOTs (Scheme 2).

With the optimized reaction conditions being identified (Table 1, entry 13), we examined the scope of secondary and primary alkyl bromides (Figure 2). A variety of cyclic and open-chain secondary and primary halides were competent with the

**Scheme 2. Coupling of 1 with Other Methyl Sulfonates**



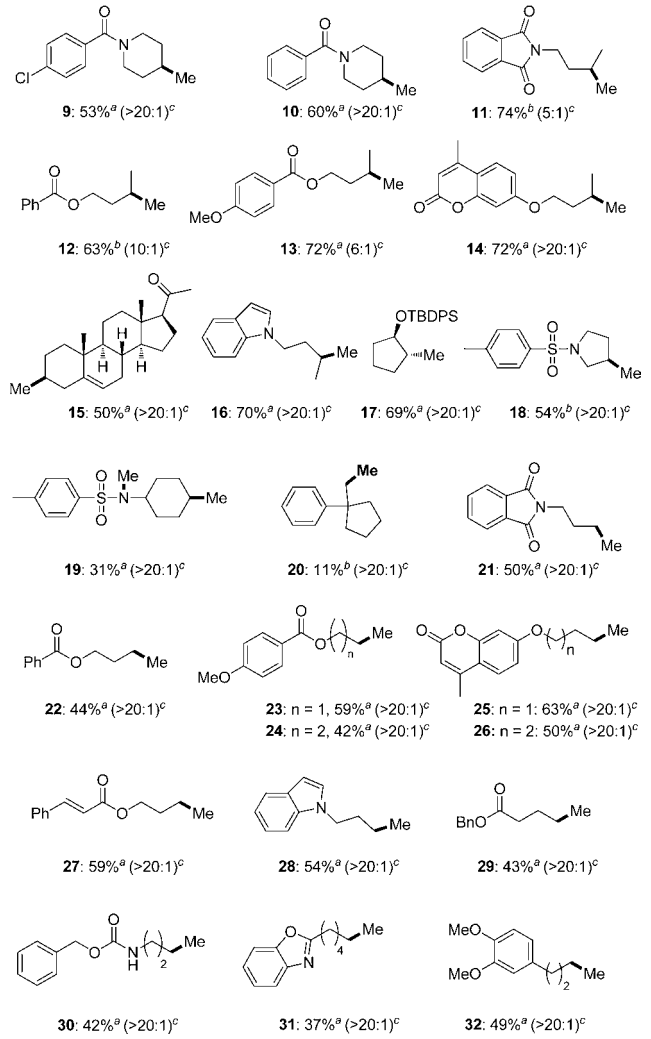




**Figure 2.** Examples of methylation of various alkyl halides. (a) Isolated yields. (b) Yields were determined by $^1H$ NMR analysis of an inseparable mixture of product and hydrodehalogenation byproduct using PhTMS as internal standard (calibrated). (c) The ratio of product to hydrodehalogenation byproduct was determined by $^1H$ NMR analysis.

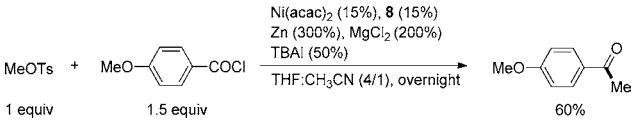
reductive coupling conditions, generally giving methylation products **9–18** in moderate to good yields, where a wide range of functional groups including ester, ketone, indole, phthalimide, and sterically dense 2-TBDPS-protected silyl ether are tolerated. 3-Methyl-1-tosylpyrrolidine **18** was also achieved in moderate yield, where the bromo substrate often suffers from a $\beta$-H elimination issue. The unprotected TsNH group underwent methylation on the nitrogen as evident in **19**, which consequently resulted in a poor yield for **19**. While the sterically more hindered primary alkyl bromides, e.g., **20**, gave poor coupling yield, moderate to good yields for the methylation of less hindered primary bromides were generally observed, e.g., in **21–32**. Interestingly, the Cbz-protected free amine did not undergo *N*-methylation as evident in **30**. Again, excellent


dx.doi.org/10.1021/ol502682q | *Org. Lett.* 2014, 16, 5620–5623

functional group compatibility was observed for methylation of primary alkyl bromides including conjugated alkene as in **27**.

Similarly, with MeOTs being the methylation reagent, we examined the possibility of methylation of allylic carbonate, aryl bromide, and acid chlorides under the standard conditions developed by our laboratory (Scheme S1, Supporting Information).[9b,d,e,15,16] Whereas the allyl and aryl electrophiles failed to generate methylation products (Scheme S1, Supporting Information), 4-Methoxy benzoyl chloride provided the desired ketone product in 27% yield in the presence of $Bu_4NI$ (Scheme S1, Supporting Information).[16] Extensive optimization of the reaction parameters enabled us to boost the yield to 60% by using 15% of $Ni(acac)_2$, 15% of 5,5′-dimethyl-2,2′-bipyridine (**8**), and 1.5 equiv of acid chlorides and $MgCl_2$ in $THF/CH_3CN$ (v/v, 4:1) (Scheme 3).

**Scheme 3. Optimized Reaction Conditions for Methylation of 4-Methoxybenzoyl Chloride**




Application of the optimized methyl ketone formation conditions to a variety of aryl acid chlorides were explored, generating **33**−**43**. In general, the aryl rings bearing electron-donating substituents displayed better coupling efficiency than those containing electron-withdrawing groups by delivering moderate to good yields as evident in Figure 3. The use of methyl

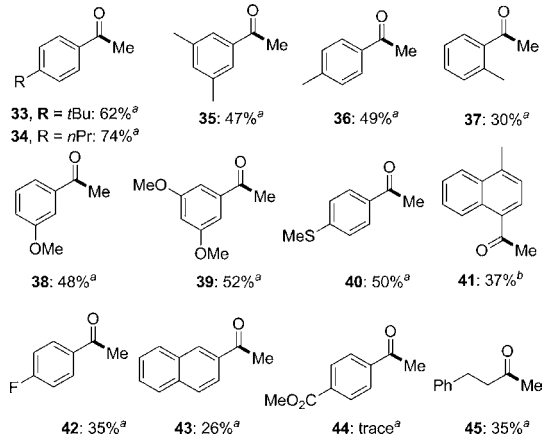
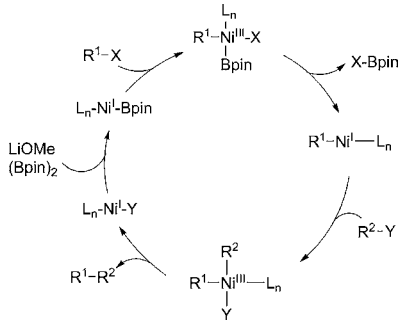



**Figure 3.** Examples of methylation of various aryl acid chlorides. (a) Isolated yields. (b) Yields were determined by $^1H$ NMR analysis using PhTMS as an internal standard (calibrated).

4-(chlorocarbonyl)benzoate only resulted in a trace amount of ketone product **44**. Finally, the alkyl acid, e.g., 3-phenylpropanoyl chloride, only provided the ketone **45** in low yield.

In our previous studies, we have demonstrated that under the $Ni/(Bpin)_2$ reductive coupling conditions in situ formation of alkyl-Bpin followed by Suzuki mechanism is not operative.[14] Similarly, we have also illustrated that the coupling of alkyl-Zn reagents with aryl acid chlorides is a slower process than reductive coupling ketone formation.[9c,b] Indeed, while MeBpin did not give the coupling product, MeZnI was much less effective than MeOTs.[16] Consequently, we believe that the present methylation of alkyl halides should not involve in situ formation of methyl-Bpin.[17] In the reductive ketone-forming process, the formation of methyl-Zn reagent cannot be excluded, but it should not dominate the reaction process. The reason why MeOTs is suited for methylation is possibly due to relatively slow formation of MeX (X = Cl, Br arising from $NiCl_2$ or alkyl bromides) under the conditions of methylation of alkyl halides and MeI in ketone formation, which avoids rapid dimerization of MeX (X = I, Cl, Br) due to their low concentrations. This hypothesis is in agreement with our previously proposed mechanisms for alkyl−alkyl (Ni/Bpin) and ketone-forming reactions.[9b,14] The former case involves oxidative addition of first $R^1_{alkyl}$−X to Ni(I)−Bpin followed by reductive elimination of Bpin−X to give $R^1_{alkyl}$−Ni(I). Subsequent oxidative addition of $R^2_{alkyl}$−X to $R^1_{alkyl}$−Ni(I) gives $R^1_{alkyl}$−Ni(III)− $R^2_{alkyl}$, which delivers the product upon reductive elimination (Scheme 4).[14] Successful cross-coupling of

**Scheme 4. Proposed Catalytic Cycle for Methylation of Alkyl Halides**




two alkyl halides would require a matched oxidative addition rates for the two coupling partners. Therefore, a low concentration of MeX (X = Cl, Br) should guarantee a low oxidative addition rate for MeX so as to match the oxidative addition rate for a second yet more hindered alkyl halide. Consequently, rapid dimerization of MeX can be avoided. For ketone synthesis, the proposed mechanism suggests that oxidative addition of acid chlorides to Ni(0) needs to be faster than that of MeX.[9b] A low concentration of MeX (X = I) is therefore pivotal to reduce the oxidative addition rate of MeX to Ni(0).

In summary, we have identified methyl tosylate as an excellent methylation reagent for reductive coupling with unactivated alkyl halides and aryl acid chlorides, which allows efficiently installation of a methyl group for alkyl−methyl and ketone formation. The reactions avoid in situ formation of methyl zinc reagents which generally inhibit the reductive coupling process. The easy-to-operate and mild conditions may provide applications for preparation of compounds of interests.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

### Corresponding Authors

*E-mail: khlin@shu.edu.cn.
*E-mail: Hegui_gong@shu.edu.cn.

### Author Contributions

§Z.L. and W.X. contributed equally.


dx.doi.org/10.1021/ol502682q | Org. Lett. 2014, 16, 5620−5623

## Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

Dr. Hongmei Deng (Shanghai University) is thanked for use of the NMR facility. Financial support was provided by the Chinese NSF (Nos. 21172140 and 21372151) and the Program for Professor of Special Appointment at Shanghai Institutions of Higher Learning (Dongfang Scholar) Shanghai Education Committee.

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