# Room Temperature Nickel(0)-Catalyzed Suzuki–Miyaura Cross-Couplings of Activated Alkenyl Tosylates: Efficient Synthesis of 4-Substituted Coumarins and 4-Substituted 2(*5H*)-Furanones

Zhen-Yu Tang, Qiao-Sheng Hu*

Department of Chemistry, College of Staten Island and the Graduate Center of the City University of New York, Staten Island, NY 10314, USA
Fax: (+1)-718-982-3910, e-mail: qiaohu@mail.csi.cuny.edu

Received: June 1, 2004; Accepted: August 8, 2004

**Abstract:** Room temperature nickel(0)/tricyclohexylphosphine [Ni(0)/$PCy_3$]-catalyzed Suzuki–Miyaura cross-couplings of 4-(*p*-toluenesulfonyloxy)coumarins and 4-(*p*-toluenesulfonyloxy)-2(*5H*)-furanone with arylboronic acids are described in this communication. Our study shows that activated alkenyl tosylates possess higher activities than aryl tosylates in the Suzuki–Miyaura cross-couplings. The mild reaction conditions and the high efficiency of the Ni(0)/$PCy_3$ catalyst make it very useful in the synthesis of 4-substituted coumarins and 4-substituted 2(*5H*)-furanones, two families of biologically important molecules.

**Keywords:** arylboronic acids; cross-coupling; nickel; phosphane ligand; tosylates

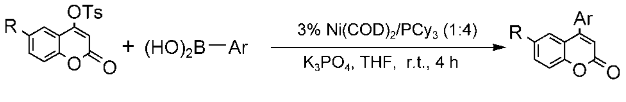
4-Substituted coumarins and 4-substituted 2(*5H*)-furanones are two families of biologically important molecules with interesting biological properties, including anti-HIV and antibiotic activities.[1,2] A number of methods have been developed for their synthesis in the past years. Among the various methods reported, transition metal-catalyzed cross-couplings of 4-(*p*-toluenesulfonyloxy)coumarin and 4-(*p*-toluenesulfonyloxy)-2(*5H*)-furanone with arylboronic acids are especially attractive approaches due to the readily accessibility of 4-(*p*-toluenesulfonyloxy)coumarin and 4-(*p*-toluenesulfonyloxy)-2(*5H*)-furanone, and the air-stable, non-toxic nature of arylboronic acids.[3–7] In this context, Yang and coworkers reported the palladium(0)-catalyzed Suzuki–Miyaura cross-couplings of 4-(*p*-toluenesulfonyloxy)coumarin and 4-(*p*-toluenesulfonyloxy)-2(*5H*)-furanone.[4a–c,7a] However, their reaction protocol requires heating in basic aqueous solution, which may be detrimental to the α,β-unsaturated ester functional groups, and lengthy reaction time as well as relatively high palladium loading (5%). The search for more efficient methods for the synthesis of these biologically promising compounds continues.

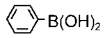
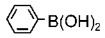
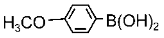
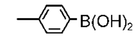
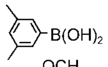
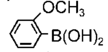
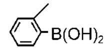
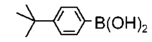
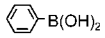
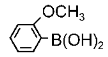
In our laboratory, we have initiated a project to explore the synthetic utilization of less studied aryl/alkenyl arenesulfonates, which are readily accessible from phenols or enols and arenesulfonyl chlorides. Recently, we have demonstrated the room temperature Ni(0)/$PCy_3$-catalyzed cross-coupling reactions of aryl *p*-toluenesulfonates with arylboronic acids.[8] The mild conditions (room temperature, THF as solvent and $K_3PO_4$ as base) of the Ni(0)/$PCy_3$ catalyst system, which might be more compatible with α,β-unsaturated ester functional groups, led us to undertake Ni(0)/$PCy_3$-catalyzed cross-coupling reactions of activated alkenyl tosylates, particularly the readily accessible 4-(*p*-toluenesulfonyloxy)coumarin and 4-(*p*-toluenesulfonyloxy)-2(*5H*)-furanone, with arylboronic acids. In this communication, our results are reported.

Our study began with the cross-coupling of 4-(*p*-toluenesulfonyloxy)coumarin with phenylboronic acid. We found that under our catalyst protocol {3% of bis(1,5-cyclopentadiene)nickel(0) [$Ni(COD)_2$]/12% $PCy_3$, 3 equivs. of potassium phosphate ($K_3PO_4$) as base, tetrahydrofuran (THF) as solvent}, the reaction went to completion within 4 h at room temperature and the desired product was isolated in 94% yield. This result not only established the feasibility of employing Ni(0)/$PCy_3$ as an efficient catalyst for the cross-coupling of 4-(*p*-toluenesulfonyloxy)coumarin with arylboronic acids under mild conditions, but also suggested that 4-(*p*-toluenesulfonyloxy)coumarin was more reactive than aryl tosylates, which required 8 h to go to completion under otherwise identical conditions. A number of arylboronic acids have thus been employed for the cross-couplings and our results are listed in Table 1. As shown in Table 1, complete conversions, as well as excellent isolated yields, were observed for all the boronic acids employed although an extended reaction time was needed for sterically hindered boronic acids (Table 1, entries 7 and 8).

DOI: 10.1002/adsc.200404150

**Table 1.** Room temperature Ni(0)-catalyzed Suzuki cross-coupling reactions of 4-(*p*-toluenesulfonyloxy)coumarins.[a]



| Entry | R | Ar-B(OH)$_2$ | Yield [%][b,c] |
|---|---|---|---|
| 1 | H |  | 94 |
| 2 | H |  | 90[e] |
| 3 | H |  | 93 |
| 4 | H |  | 93 |
| 5 | H |  | 90 |
| 6 | H |  | 91 |
| 7 | H |  | 91[d] |
| 8 | H |  | 86[d] |
| 9 | $CH_3$ |  | 90 |
| 10 | $CH_3$ |  | 84[d] |

[a] Reaction conditions: tosylate (1.0 equiv.), arylboronic acids (1.5 equivs.), Ni(COD)$_2$/PCy$_3$ (3 mol %/12 mol %), K$_3$PO$_4$ (3 equivs.), THF (2 mL), room temperature.

[b] Isolated yields (average of two runs).

[c] Refs.[4a, b]

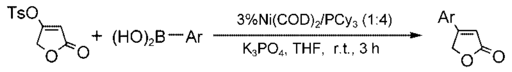
[d] Reaction time: 8 h (not minimized).

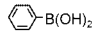
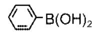
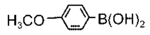
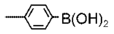
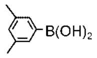
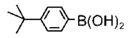
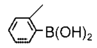
[e] 3 mol % Ni(PCy$_3$)$_2$Cl$_2$/*n*-BuLi was used as catalyst.

We have also sought to use the air-stable bis(tricyclohexylphosphine)nickel(II) chloride [Ni(PCy$_3$)$_2$Cl$_2$][9] as catalyst precursor to substitute the air-sensitive Ni(COD)$_2$. We found that although Ni(PCy$_3$)$_2$Cl$_2$ and Ni(PCy$_3$)$_2$Cl$_2$/2 PCy$_3$ were ineffective for the cross-coupling of 4-(*p*-toluenesulfonyloxy)coumarin with phenylboronic acid, likely due to their inability to generate the catalytically active Ni(0) species under the reaction conditions, the catalyst generated from Ni(PCy$_3$)$_2$Cl$_2$/*n*-BuLi was as efficient as that of Ni(COD)$_2$/PCy$_3$ (Table 1, entry 2).

Our success in Ni(0)/PCy$_3$-catalyzed Suzuki–Miyaura cross-couplings of 4-(*p*-toluenesulfonyloxy)coumarins suggested that the Ni(0)/PCy$_3$ catalyst system should also be effective for the cross-couplings of other activated alkenyl tosylates with arylboronic acids. We have thus also carried out the Ni(0)/PCy$_3$-catalyzed cross-coupling reactions of 4-(*p*-toluenesulfonyloxy)-2(*5H*)-furanone with arylboronic acids. It was found that 4-(*p*-toluenesulfonyloxy)-2(*5H*)-furanone indeed coupled smoothly with arylboronic acids under our reaction condition (Table 2). The Ni(0)/PCy$_3$ catalyst generated from Ni(PCy$_3$)$_2$Cl$_2$/*n*-BuLi has also been tested and it also showed a similar efficiency as that of Ni(COD)$_2$/PCy$_3$ (Table 2, entry 2).

**Table 2.** Room temperature Ni(0)-catalyzed Suzuki cross-coupling reactions of 4-(*p*-toluenesulfonyloxy)-2(*5H*)-furanone.[a]



| Entry | Ar-B(OH)$_2$ | Yield [%][b,c] |
|---|---|---|
| 1 |  | 92 |
| 2 |  | 91[d,e] |
| 3 |  | 77 |
| 4 |  | 80 |
| 5 |  | 73 |
| 6 |  | 55[d] |
| 7 |  | 77[d] |

[a] Reaction conditions: tosylate (1.0 equiv.), arylboronic acids (1.5 equivs.), Ni(COD)$_2$/PCy$_3$ (3 mol %/12 mol %), K$_3$PO$_4$ (3 equivs.), THF (2 mL), room temperature.

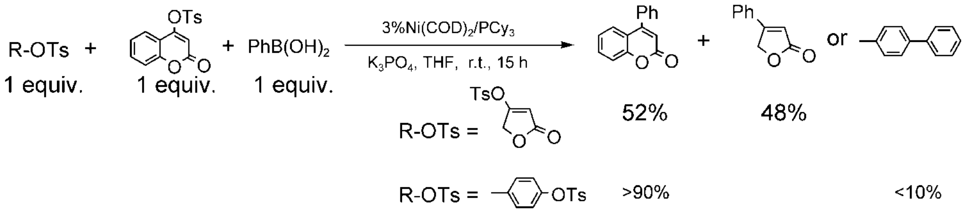
[b] Isolated yields (average of two runs).

[c] Refs.[7a]

[d] Reaction time: 8 h (not minimized).

[e] 3% Ni(PCy$_3$)$_2$Cl$_2$/*n*-BuLi was used as catalyst.

We have also carried out a reactivity study for 4-(*p*-toluenesulfonyloxy)coumarin, 4-(*p*-toluenesulfonyloxy)-2(*5H*)-furanone and *p*-tolyl tosylate. We found that when the mixture of 4-(*p*-toluenesulfonyloxy)coumarin (1 equiv.) and 4-(*p*-toluenesulfonyloxy)-2(*5H*)-furanone (1 equiv.) reacted with phenylboronic acid (1 equiv.), almost a 1:1 ratio of the corresponding products were formed. This suggests that the reactivities of 4-(*p*-toluenesulfonyloxy)coumarin and 4-(*p*-toluenesulfonyloxy)-2(*5H*)-furanone are similar to each other. On the other hand, reaction of *p*-tolyl tosylate (1 equiv.) and 4-(*p*-toluenesulfonyloxy)coumarin (1 equiv.) with phenylboronic acid (1 equiv.) yielded the corresponding cross-coupling products in a 1:9 ratio. These results im-



**Scheme 1.** Ni(0)-catalyzed cross-couplings of *p*-tolyl tosylate, 4-(*p*-toluenesulfonyloxy)coumarin, 4-(*p*-toluenesulfonyloxy)-2(*5H*)-furanone with phenylboronic acid.

ply that 4-(*p*-toluenesulfonyloxy)coumarin and 4-(*p*-toluenesulfonyloxy)-2(*5H*)-furanone are more reactive than *p*-tolyl tosylate (Scheme 1).

In summary, we have demonstrated that Ni(0)/$PCy_3$ is a highly active catalyst system for the room temperature Suzuki–Miyaura coupling of the readily accessible 4-(*p*-toluenesulfonyloxy)coumarin and 4-(*p*-toluenesulfonyloxy)-2(*5H*)-furanone with arylboronic acids. Our study showed that the electron-withdrawing group-substituted alkenyl tosylates possess higher activities than aryl tosylates. The mild reaction conditions, the high efficiency and the easy availability of the Ni(0)/$PCy_3$ catalyst make this catalyst system very useful in the synthesis of biologically important 4-substituted coumarins and 4-substituted 2(*5H*)-furanones. It is believed that the Ni(0)/$PCy_3$ catalyst system could be extended for the cross-couplings of other alkenyl sulfonates. Work along this line is underway.

## Experimental Section

### General Procedure for the Ni(0)/$PCy_3$-Catalyzed Suzuki–Miraura Couplings of 4-(*p*-Toluenesulfonyloxy)coumarin and 4-(*p*-Toluenesulfonyloxy)-2(*5H*)-furanone

***Method A:*** In a glove-box with an $N_2$ atmosphere, to a mixture of phenylboronic acid (1.5 mmol), potassium phosphate (3 mmol), 4-(*p*-toluenesulfonyloxy)coumarins or 4-(*p*-toluenesulfonyloxy)-2(*5H*)-furanone (1 mmol) and 2 mL THF were added bis(1,5-cyclopentadiene)nickel(0) (8.3 mg, 0.03 mmol) and tricyclohexylphosphine (33 mg, 0.12 mmol). The mixture was allowed to stir for 4 to 8 hours. After quenching with water, the reaction mixture was extracted with ethyl acetate. The organic phase was washed with brine and the solvent was evaporated under vacuum. Flash chromatography on the silica gel (hexane:ethyl acetate = 90:10 to 85:15) yielded the cross-coupling products.

***Method B:*** In a glove-box with an $N_2$ atmosphere, to a mixture of bis(tricyclohexylphosphine)nickel(II) chloride (11 mg, 0.015 mmol), tricyclohexylphosphine (0.03 mmol ), were added 2 mL THF. After the Ni(II) species had dissolved, *n*-butyllithium (20 μL, 2.5 M in hexane) was added. After stirring for 1 minute, to the deep red solution were added phenylboronic acid (0.75 mmol), potassium phosphate (1.5 mmol) and the 4-(*p*-toluenesulfonyloxy)coumarin or 4-(*p*-toluenesulfonyloxy)-2(*5H*)-furanone (0.5 mmol) sequentially. The mixture was allowed to stir for 4 hours. After quenching with water, the reaction mixture was extracted with ethyl acetate. The organic phase was washed with brine and the solvent was evaporated under vacuum. Flash chromatography on silica gel (hexane: ethyl acetate = 90:10 to 85:15) yielded the cross-coupling products.

## Acknowledgements

*We thank the National Institutes of Health (GM69704) for supporting this work. Partial support from the Professional Staff Congress-CUNY Research Award Programs is also gratefully acknowledged.*

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