A new protocol for synthesizing diarylmethanes using a benzyltitanium reagent as a nucleophile

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Abstract

The first palladium-catalyzed cross-coupling of various substituted benzyltitaniums with aryl triflates is presented for the synthesis of diarylmethanes in yields of up to 94% through highly selective C–O bond functionalization. The benzyltitaniums act as nucleophiles to realize the C(sp²)–C(sp³) cross-coupling with high efficiency in short reaction times. The reactions proceed at 60°C and show excellent functional groups tolerance.

Keywords

aryl triflates, benzyltitanium reagents, cross-coupling, diarylmethanes, palladium catalysis

Introduce

Palladium-catalyzed cross-coupling plays an important role in the industrial manufacture of pharmaceuticals, fine chemicals, and materials. Researchers have found that a significant number of bioactive molecules contain a methylene functional group, which makes research on diarylmethane-containing compounds important (Figure 1). The preparation of diarylmethanes is usually accomplished by four common methods: (a) electrophilic substitution of aromatics, which is often referred to as Friedel–Crafts benzylation but suffers from poor regioselectivity; (b) nucleophilic aromatic substitution reactions with benzyl derivatives as nucleophiles; (c) C–H activation of aromatic hydrocarbons; and (d) the most commonly used strategy to prepare diarylmethanes through transition metal-catalyzed coupling by employing either electrophilic benzyl derivatives or nucleophilic benzyl reagents. More recently, organotitanium reagents have been used as organometallic partners in C(sp²)–C(sp³) and C(sp³)–C(sp³) cross-coupling reactions. Organotitanium reagents have lower nucleophilicity, basicity, and better functional group tolerance compared with Grignard reagents. Moreover, compared with organozinc reagents, organotitanium reagents have higher metal transfer rates. Studies by Dastbaravardeh and Knochel have shown that the reactivity of organotitanium reagents as nucleophiles is much higher than that of the corresponding organozinc counterparts.

Interestingly, although many exciting achievements have been made in nucleophilic addition of organotitanium reagents to carbonyl compounds (Scheme 1a), a new protocol for synthesizing diarylmethanes using a benzyltitanium reagent as a nucleophile has been presented.
by comparison, much less attention has been devoted to the employment of such reagents in C(sp²)–C(sp²) cross-coupling transformations (Scheme 1b). Furthermore, there is only one successful example of the employment of such reagents in C(sp²)–C(sp³) cross-coupling transformations (Scheme 1c). To the best of our knowledge, this is the first example using organotitanium nucleophiles to generate diarylmethane units by C(sp²)–C(sp³) cross-coupling reactions (Scheme 1d).

Organic halides are commonly the electrophiles, which generate halogenated waste after reactions. Also, halides are sometimes limited by reaction conditions, making it difficult to use them in some advanced synthetic intermediates; these shortcomings can be solved using alternative partners, such as C–O electrophiles. Aryl triflates are popular as electrophiles in transition metal-catalyzed cross-coupling reactions because they are derived from readily available phenols and carbonyl enolates. However, phenolic hydroxy and carbonyl moieties are more common organic functional groups than non-commercially available aryl halides. Herein, we present the first palladium-mediated cross-coupling of benzyltitanium reagents with aryl triflates to give the corresponding diarylmethanes in yields of up to 94%.

Figure 1. Examples of the diarylmethane motif in pharmaceuticals.

Scheme 1. Comparison of reported methods and our design.
Results and discussion

To develop a new C(sp<sup>2</sup>)–C(sp<sup>3</sup>) cross-coupling catalyzed protocol, we initially used phenyl triflate (1a) in a reaction with [(4-(ethoxycarbonyl)benzyl)trisopropoxytitanium (2a)] for optimizing the reaction conditions. The results are given in Table 1. In the absence of a transition metal catalyst and ligand, no product formation was observed (Table 1, Entry 1).

The use of various phosphine ligands subsequently tested at a temperature of −10°C using 3 mol% of Pd(OAc)<sub>2</sub> as the catalyst. The results showed that the highest yield of product 3aa was obtained with ligand L<sub>4</sub>, which afforded 3aa in 73% yield. To increase the amount of the coupling product, other palladium catalysts were studied. The results show that Pd(PPh)<sub>3</sub> and Pd<sub>2</sub>(dbb) gave poor yields in contrast to Pd(OAc)<sub>2</sub> (Table 1, Entries 10 and 11). Further studies with varying ratio of Pd(OAc)<sub>2</sub> and L<sub>4</sub> led to a satisfactory yield of 82% when a ratio of 1:2 was employed (Table 1, Entry 12). Next the reaction solvent was screened, and the results showed that the use of a co-solvent of THF/DME (1:2) was the best choice (Table 1, Entry 19), affording product 3aa in 87% yield.

While the effects of additives on the coupling reactions were important, LiCl proved to be the additive of choice.

Table 1. Optimization of the reaction conditions:<sup>a</sup>

| Entry | Catalyst     | Ligand | Pd/ligand | Additive | Solvent              | Time (h) | Yield (%)<sup>b</sup> |
|-------|--------------|--------|-----------|----------|----------------------|---------|----------------------|
| 1     | –            | –      | –         | –        | THF                  | 24      | n.d.                 |
| 2     | Pd(OAc)<sub>2</sub> | PPh<sub>3</sub> | 1:2       | –        | THF                  | 24      | n.d.                 |
| 3     | Pd(OAc)<sub>2</sub> | PCy<sub>3</sub> | 1:2       | –        | THF                  | 24      | 15                   |
| 4     | Pd(OAc)<sub>2</sub> | L<sub>1</sub> | 1:1       | –        | THF                  | 24      | 43                   |
| 5     | Pd(OAc)<sub>2</sub> | L<sub>2</sub> | 1:1       | –        | THF                  | 24      | 49                   |
| 6     | Pd(OAc)<sub>2</sub> | L<sub>3</sub> | 1:1       | –        | THF                  | 24      | 61                   |
| 7     | Pd(OAc)<sub>2</sub> | L<sub>4</sub> | 1:1       | –        | THF                  | 24      | 73                   |
| 8     | Pd(OAc)<sub>2</sub> | L<sub>5</sub> | 1:1       | –        | THF                  | 24      | 64                   |
| 9     | Pd(OAc)<sub>2</sub> | L<sub>6</sub> | 1:1       | –        | THF                  | 24      | 66                   |
| 10    | Pd(OAc)<sub>2</sub> | L<sub>4</sub> | 1:1       | –        | THF                  | 24      | 25                   |
| 11    | Pd(PPh)<sub>3</sub> | L<sub>4</sub> | 1:1       | –        | THF                  | 24      | 41                   |
| 12    | Pd(OAc)<sub>2</sub> | L<sub>4</sub> | 1:2       | –        | THF                  | 24      | 82                   |
| 13    | Pd(OAc)<sub>2</sub> | L<sub>4</sub> | 1:3       | –        | THF                  | 24      | 81                   |
| 14    | Pd(OAc)<sub>2</sub> | L<sub>4</sub> | 1:2       | –        | Toluene              | 24      | <5                   |
| 15    | Pd(OAc)<sub>2</sub> | L<sub>4</sub> | 1:2       | –        | 1,4-dioxane          | 24      | 37                   |
| 16    | Pd(OAc)<sub>2</sub> | L<sub>4</sub> | 1:2       | –        | DME                  | 24      | 80                   |
| 17    | Pd(OAc)<sub>2</sub> | L<sub>4</sub> | 1:2       | –        | Et<sub>2</sub>O      | 24      | 32                   |
| 18    | Pd(OAc)<sub>2</sub> | L<sub>4</sub> | 1:2       | –        | THF/DME (1:3)        | 24      | 75                   |
| 19    | Pd(OAc)<sub>2</sub> | L<sub>4</sub> | 1:2       | –        | THF/DME (1:2)        | 24      | 87                   |
| 20    | Pd(OAc)<sub>2</sub> | L<sub>4</sub> | 1:2       | –        | THF/DME (1:1)        | 24      | 79                   |
| 21<sup>c</sup> | Pd(OAc)<sub>2</sub> | L<sub>4</sub> | 1:2 | LiCl | THF/DME (1:2) | 6 | 85 |
| 22<sup>c</sup> | Pd(OAc)<sub>2</sub> | L<sub>4</sub> | 1:2 | LiBr | THF/DME (1:2) | 6 | 61 |
| 23<sup>c</sup> | Pd(OAc)<sub>2</sub> | L<sub>4</sub> | 1:2 | LiCl | THF/DME (1:2) | 8 | 92 (89%)<sup>d</sup> |
| 24<sup>c</sup> | Pd(OAc)<sub>2</sub> | L<sub>4</sub> | 1:2 | LiCl | THF/DME (1:2) | 10 | 92 |
| 25<sup>c</sup> | Pd(OAc)<sub>2</sub> | L<sub>4</sub> | 1:2 | LiCl | THF/DME (1:2) | 4 | 67 |

<sup>a</sup>Reaction conditions: 1a (0.5 mmol), 2a (0.6 mmol), solvent (3.0 mL), −10°C.

<sup>b</sup>G C yield calibrated against tridecane as an internal standard, n.d. = not detected.

<sup>c</sup> The additive (1.2 equiv.) was added and the reaction was run at 60°C.

<sup>d</sup> Isolated yield is given in parentheses.
Table 2. Scope of the cross-coupling of aryl triflates 1 with benzyltitanium·lithium chloride 2a,b.

| Reaction conditions: 1 (0.5 mmol), 2 (0.6 mmol), Pd(OAc)₂ (3 mol%, with respect to 1), L₄ (6 mol%), THF/DME (1:2, 3.0 mL), 60°C, 8 h, Ar atmosphere. | Isolated yields. |

Scheme 2. Chemoselective cross-coupling.
Its use increased the reaction activity and shortened the reaction time (Table 1, Entry 21). Finally, extending the reaction time to 8 h increased the reaction yield to 92% (Table 1, Entry 23).

On the basis of the optimized reaction conditions, we next investigated the scope and generality of the cross-coupling reactions of a range of aryl triflates with different benzyltitanium lithium chloride species, and the results are given in Table 2. First, we studied the influence of the functional group on the aryl triflate. Reactions with non-activated aryl triflates proceeded satisfactorily. Phenyl triflate \((\text{1a})\) reacted with \([(4-\text{ethoxycarbonyl})\text{benzyl}]\text{triisopropoxytitanium·lithium chloride}\) \((\text{2a})\) to give the coupling product \((\text{3aa})\) in 89% isolated yield. The result of the reaction with o-tolyltriflate was comparable to those with p- and m-tolyltriflate, and an 81% yield of the coupling product \((\text{3da})\) was obtained, indicating that the reaction was not affected by steric hindrance. Conversely, the reactions with deactivated aryl triflates were less efficient and were not ideal with the substituted phenyl triflates \((\text{1e, f})\) possessing a p-methoxy or p-dimethylamine group giving 74% and 61% yields of products \((\text{3ea and 3fc})\). When the aryl triflate was substituted with an electron-withdrawing group, the reactions proceeded efficiently: trifluoromethyl-, fluoro- and chloro-substituted aryl triflates reacted to give excellent yields of the cross-coupled products \((\text{3ga, 3ha, 3ia, and 3ja})\). The reactions of electron-deficient phenyl triflates substituted with p-cyano \((\text{2k})\), m-cyano \((\text{2l})\), p-N, N-dimethylaniline amide \((\text{2m})\), and o- and m-acetyl groups \((\text{2n and 2o})\) produced good-to-excellent isolated yields of the corresponding functionalized diarylmethanes \((\text{3ka-oa})\) with benzyltitanium \((\text{2a})\). The reaction of 1-naphthyltriflate with \((\text{2a})\) afforded a good yield of the desired product \((\text{3pa})\). Also, screening of heteroaryl triflates \((\text{1q, 1r, and 1s})\) showed that excellent yields were obtained. Similarly, we also examined the cross-coupling reactions of phenyltrflate \((\text{2a})\) with different benzyltitaniums and obtained the corresponding cross-coupling products \((\text{3ab-3ag})\) in good-to-excellent yields (Table 2). From the results, it can be seen that the reactions with different substituted benzyltitaniums was not affected by changes in the electronic properties of the aryl rings of the benzyltitaniums.

Palladium-catalyzed reactions of mixtures of phenyl triflate \((\text{1a})\) and bromobenzene \((\text{4})\) with triisopropoxy(4-methoxybenzyl)titanium·lithium chloride \((\text{2g})\) were also examined \((\text{2a})\). The results showed that bromobenzene showed slightly lower reactivity under the conditions. Furthermore, 2-pyridyl triflate \((\text{1q})\) proved to be more reactive (Scheme 2b). Thus, 2-pyridyl triflate \((\text{1q})\) could be chemoselectively coupled with triisopropoxy(4-methoxybenzyl)titanium reagent in the presence of phenyl triflate \((\text{1a})\).

We propose the possible reaction mechanism shown in Scheme 3. First, oxidative addition of Pd(0) to the aryl triflate \((\text{1})\) occurs. This is followed by transmetallation of intermediate \((\text{A})\) with the organotitanium reagent \((\text{2})\), to yield intermediate \((\text{B})\). Finally, reductive elimination generates the desired Coupling product \((\text{3})\) and Pd(0), which completes the catalytic cycle.

**Conclusion**

In conclusion, we have developed the first examples of the palladium-catalyzed reactions of benzyltitanium reagents with aryl triflates to give diarylmethane derivatives. The procedure demonstrates broad suitability, being useful for the coupling of both electron-deficient and electron-rich aryl triflates. A large variety of functionalized diarylmethanes have been efficiently prepared using this methodology, which is based on the use of the commercially available catalytic system Pd(OAc)$_2$/L$_4$. Thus, the new coupling protocol involving...
palladium-catalyzed organotitanium reagents established in this study promises to provide additional opportunities for the development of organic synthesis.

**Experimental**

**General**

Anhydrous lithium chloride, Pd(OAc)\(_2\), Pd(PPh\(_3\)\(_3\))\(_2\), and Pd\(_2\)(dba)\(_3\) were purchased from Sigma-Aldrich. THF, 1,4-dioxane, and 1,2-dimethoxyethane were purchased from Alfa Aesar. Other reagents were available commercially and were used without further purification, unless otherwise indicated. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. THF was dried over alumina under N\(_2\) using a Grubbs-type solvent purification system. All benzyltitanium reagents were prepared from the corresponding benzylmagnesium halides. 4-Hydroxy-N,N-dimethylbenzamide was purchased from Alfa Aesar, and were used without further purification, unless otherwise indicated. All reactions were monitored with known compounds matched with data reported in the literature. Reactions were carried out under an argon atmosphere. All benzyltitanium reagents were prepared from functionalized aryl Grignard reagents, including 4-cyanobenzylmagnesium chloride, were prepared by iodine–magnesium exchange using i-PrMgCl•LiCl (functionalized Grignard reagents were cooled to −20°C). Aryl Grignard reagents, such as benzyltitanium reagents, were purified by column chromatography on silica gel (300–400 mesh).

**Experimental section**

**General procedure A: benzyltitanium reagents.** The glassware was oven-dried (100°C) and cooled under a stream of argon gas. Aryl Grignard reagents, such as benzylmagnesium chloride and 4-methoxybenzylmagnesium chloride, were prepared by iodine–magnesium exchange using i-PrMgCl•LiCl according to Knochel method. All of the Grignard reagents were titrated before use. The Grignard reagent (20 mmol) was cooled to 0°C and was used without further purification, unless otherwise indicated. THF was dried over alumina under N\(_2\) using a Grubbs-type solvent purification system. All benzyltitanium reagents were prepared from the corresponding benzylmagnesium halides. 4-Hydroxy-N,N-dimethylbenzamide was purchased from Alfa Aesar, and were used without further purification, unless otherwise indicated. All reactions were monitored with known compounds matched with data reported in the literature. Reactions were carried out under an argon atmosphere. All benzyltitanium reagents were prepared from functionalized aryl Grignard reagents, including 4-cyanobenzylmagnesium chloride, were prepared by iodine–magnesium exchange using i-PrMgCl•LiCl (functionalized Grignard reagents were cooled to −20°C). Aryl Grignard reagents, such as benzyltitanium reagents, were purified by column chromatography on silica gel (300–400 mesh).

**General procedure B: palladium-catalyzed cross-coupling of aryl triflates with benzyltitanium reagents.** In a glovebox, the aryl triflate (0.50 mmol), Pd(OAc)\(_2\) (3 mol%), and L\(_4\) (6 mol%) were added to a dried two-necked round-bottom reaction flask equipped with an addition funnel. The reaction mixture was warmed to −10°C and allowed to react for 4 h. The volatile material was removed completely under reduced pressure, and under a nitrogen atmosphere, the residue was extracted with n-hexane (3 × 40 mL). The combined hexane solution was concentrated and was cooled to −20°C, furnishing the aryliodos(2-propoxy)titanium species as a solid product.

**Ethyl 4-{[(4-Dimethylamino)benzyl]benzoate (3fa):** Purification using silica gel column chromatography (petroleum ether/EtOAc = 3:1, v/v) afforded the desired product in a 61% yield (70.8 mg), colorless oil. HRMS (ESI) calc. for C\(_{22}\)H\(_{21}\)NO\(_2\) [M + H\(^+\)]\(^+\): m/z 284.1572 found 284.1574.

**Ethyl 4-{[(4-Dimethylcarbamoyl)benzyl]benzoate (3ma):** Purification using silica gel column chromatography (petroleum ether/EtOAc = 3:1, v/v) afforded the desired product in a 81% yield (126.0 mg), colorless oil, 1H NMR (100 MHz, CDCl\(_3\)): δ = 7.96 (d, J = 7.4 Hz, 2H), 7.20–7.14 (m, 4H), 6.99 (d, J = 7.4 Hz, 2H), 4.40 (q, J = 7.0 Hz, 2H), 3.90 (s, 2H), 3.09 (s, 6H), 1.41 (t, J = 7.2 Hz, 3H). HRMS (ESI) calc. for C\(_{18}\)H\(_{21}\)NO\(_2\) [M + H\(^+\)]\(^+\): m/z 284.1572 found 284.1574.

**Declaration of conflicting interests**

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