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Arylation and Vinylation of α-Diazocarbonyl Compounds with Boroxines

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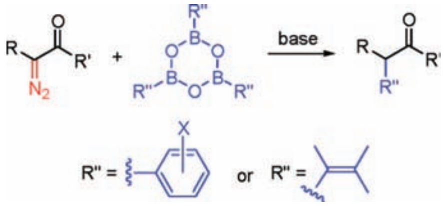
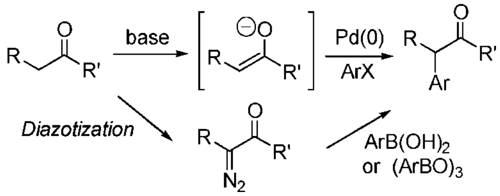
ABSTRACT



An alternative approach for α-arylation and α-vinylation of carbonyl compounds is described: reaction between aryl- or vinylboroxines with α-diazocarbonyl compounds leads to the formation of α-arylated or α-vinylated carbonyl compounds under mild conditions.

α-Arylation and α-vinylation of carbonyl compounds are very important in organic synthesis. Although various approaches have been developed for these purposes, they usually suffer drawbacks in one way or another. Recently, palladium-catalyzed α-arylation and α-vinylation of carbonyl compounds, which are mostly developed by Buchwald and Hartwig, have been shown to provide simple and efficient methods to introduce aryl and vinyl groups to the α carbon of carbonyl compounds.[1,2] However, these catalytic processes have to be carried out under strong basic conditions. An indirect approach toward α-arylated carbonyl compounds would be the arylation of the corresponding α-diazocarbonyl compounds, which could be easily available through diazotization of the corresponding carbonyl compounds under mild conditions (Scheme 1). In this paper, we report an alternative α-arylation method by the reaction of α-diazocarbonyl compounds with easily accessible arylboroxines. This approach also applies to α-vinylation by using the corresponding vinylboroxines.

Scheme 1. α-Arylation of Carbonyl Compounds



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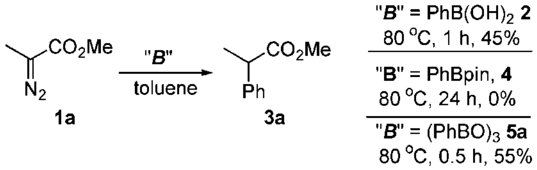
The reactions of α-diazocarbonyl compound with organoboron compounds have been previously reported to form a C−C bond between alkyl or aryl and an α carbon of carbonyl group.[3−7] Pioneering work by Hooz and co-workers established the alkylation of diazonitrile, ethyl diazoacetate, and diazoketones by means of trialkylboranes.[3] The reactions reported by Hooz are only limited to alkylboranes, and the reaction is sluggish with poor yields for organoboranes containing relatively bulky alkyl groups. Further improvement was made by Brown, Hooz, and co-workers by using dialkylchloroboranes and alkyl- or aryldichloroboranes, which are more reactive boron reagents toward diazo compounds.[4] The drawback of Brown's modification is that chlorinated byproducts are formed in some cases due to the competing 1,2-chloro migration. Particularly notable in this modification is that arylation can occur with high yields by using aryldichloroboranes,[4b] and most recently, Brown and Salunkhe have extended this reaction by using alkenyldichloroboranes.[6] However, these otherwise very attractive arylation and vinylation reactions have so far received limited attention, presumably because toxic and unstable boron compounds are used, and the reactions have to be carried out at low temperature. Moreover, in Brown's report, only ethyl diazoacetate is applied as a diazo substrate.

Mechanistically, it is reasonable to consider that these reactions are initiated by the nucleophilic attack of diazo substrate to boron. Thus, increasing the electronegativity in the boron should enhance the reaction. This explains the high reactivity with dialkylchloroboranes and alkydichloroboranes in Brown's reaction, as compared with the original trialkylboranes in Hooz's system. In view of the fact that organoboronic acids and their derivatives, which are stable, nontoxic, and easily available, are gaining popularity within the synthetic organic chemistry community,[8,9] we have conceived that it is worthwhile to investigate the reaction of diazo compounds with boronic acids and their derivatives.[10]

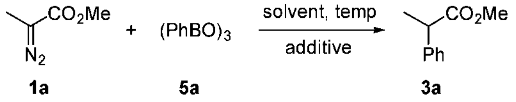
At the outset of this investigation, we examined the reaction of methyl α-diazopropionate **1a** with phenylboronic acid **2** (eq 1). The α-arylation product **3a** was isolated, albeit in low yield. Subsequent efforts to optimize this reaction proved fruitless. When phenyl pinacolborane **4** was used instead of boronic acid, **3a** was not observed, and most starting materials remained unchanged after stirring at 80 °C for 24 h. To our delight, when phenylboronic acid **2** was replaced by phenylboroxine **5a**, the reaction under the same conditions was found to be faster and the yield was slightly higher.



(1)

Further optimization of the reaction conditions was carried out. The results are summarized in Table 1. Changing solvent and temperature seemed not improve the yields (entries 1−6). It was then observed that the reaction could be significantly improved by adding base as additives, among which diisopropylamine afforded the best results (entry 11). The reaction

Table 1. Optimization of Reaction Conditions with Methyl α-Diazopropionate **1a** and Phenylboroxine **5a**[a]



entry	additive (3 equiv)	solvent	T (°C)	yield[b] (%)
1	non	PhMe	80	50
2	non	PhMe	40	33
3	non	PhH	60	31
4	non	*n*-hexane	60	24
5	non	DCE	60	30
6	Non	Et$_3$N	60	38
7	Et$_3$N	PhMe	60	72
8	pyridine	PhMe	60	68
9	morpholine	PhMe	60	60
10	^{i}Pr$_2$EtN	PhMe	60	49
11	^{i}Pr$_2$NH	PhMe	60	82
12	^{i}Pr$_2$NH	DCE	60	88
13[c]	**^{i}Pr$_2$NH**	**DCE**	**60**	**91**
14[c]	^{i}Pr$_2$NH	THF	60	85
15[d]	^{i}Pr$_2$NH	DCE	60	79

[a] If otherwise indicated, the reaction was carried out with 1.0 equiv of diazo compound, 1.5 equiv of (PhBO)$_3$. [b] Yields calculated from GC using mesitylene as an internal standard. [c] 1.0 equiv of (PhBO)$_3$ was used. [d] 0.6 equiv of (PhBO)$_3$ was used.

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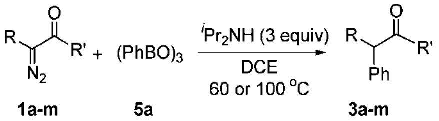
(10) For a recent report on Pd-catalyzed coupling of arylboronic acids with α-diazocarbonyl compounds, see: Peng, C.; Wang, Y.; Wang, J. *J. Am. Chem. Soc.* **2008**, *130*, 1566.

could be further improved by using 1,2-dichloroethane (DCE) as solvent (entry 13). Since three phenyl groups in one phenylboroxine can be theoretically transferred to the product, we proceeded to reduce the amount of phenylboroxine. One equivalent of boroxine afforded satifactory results (entry 13). When the phenylboroxine was further reduced, the reaction became sluggish and the yield was diminished due to the side reactions of diazo substrate (entry 15).

In Hooz and Brown's reports, only the diazo compounds without α-substitution (N_2CHA, A = CN, CO_2Et, COMe, COPh, etc.), in most cases the ethyl diazoacetate, were investigated. As a general α-arylation method, more diazo substrates with structural diversity have to be employed. Thus, the optimized reaction conditions were applied to the reaction of **5a** with various α-diazocarbonyl compounds (Table 2). The α-phenylation products were obtained in moderate to high yields in all cases. Reaction with α-alkyl substituted diazo esters gave the α-phenyl-substituted aliphatic esters in good yields (entries 2−4). When the alkyl group was replaced by hydrogen, the reaction became sluggish but the yield remained high (entries 5). Reaction with α-diazoamide also worked well (entry 6), thus providing an efficient way for α-arylation of amides.

Table 2. Reaction of **1a**−**m** with Phenylboroxine **5a**[a]



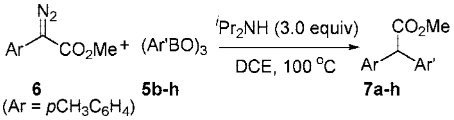
entry	diazo substrate (**1**, R, R′)	time (h)	yield[b] (%)
1	**1a**, Me, OMe	4	**3a**, 84
2	**1b**, ^{n}Pr, OMe	9	**3b**, 84
3	**1c**, ^{i}Pr, OMe	10	**3c**, 65
4	**1d**, Bn, OMe	12	**3d**, 91
5	**1e**, H, OEt	49	**3f**, 90
6	**1f**, H, N^iPr_2	48	**3e**, 96
7	**1g**, Me, C_6H	43	**3g**, 68
8	**1h**, Me, *p*-ClC_6H_4	48	**3h**, 61
9	**1i**, Me, *p*-BrC_6H_4	48	**3i**, 64
10	**1j**, C_6H_5, OMe	16	**3j**, 78
11	**1k**, *p*-$MeOC_6H_4$,OMe	2	**3k**, 81
12	**1l**, *p*-BrC_6H_4, OMe	2	**3l**, 61
13	**1m**, 1-naphthyl, OMe	17	**3m**, 56

[a] The reaction was carried out with diazo compound (1.0 equiv) and phenylboroxine (1.0 equiv) at 60 °C (for entries 1−4, 6−10) or 100 °C (entries 5, 11−13). [b] Isolated yield.

The results for the reaction with α-diazoketones are also summarized in Table 2 (entries 7−9). The slightly diminished yields in these cases as compared with α-diazoesters might be attributed to the decreased reactivity of the substrates under the reaction conditions, which resulted in 1, 2-H shift side reactions. Finally, the α-aryl-α-diazoacetates were also studied (entries 10−13). Reactions with these substrates needed a higher temperature to reach completion. The electron-donating group was found to facilitate the reaction (entry 12). Since the α-aryl-α-diazoacetates are easily available from the corresponding α-arylacetates,[11] this process constitutes a practical access to α,α-diaryl-substituted acetates.

Furthermore, a series of arylboroxines were examined through the reaction with *p*-tolyldiazoacetate **6** under the same conditions at 100 °C. As shown in Table 3, the reactions all proceeded well to afford diaryl-substituted acetate products **7a**−**h**. It was noted that the reaction was significantly accelerated by electron-withdrawing substituents of arylboroxines (entries 4−6).

Table 3. Reaction of Arylboroxine **5b**−**h** with **6**[a]

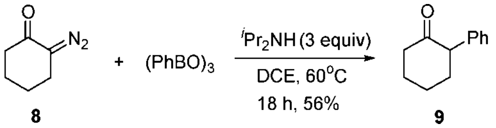


entry	**5**, Ar′	time (h)	yield (**7**, %)[b]
1	**5b**, *p*-$CH_3C_6H_4$	13	**7a**, 73
2	**5c**, *m*-$CH_3C_6H_4$	14	**7b**, 79
3	**5d**, *m*-ClC_6H_4	14	**7c**, 86
4	**5e**, *m*,*p*-$Cl_2C_6H_3$	4	**7d**, 87
5	**5f**, *m*-$NO_2C_6H_4$	2	**7e**, 87
6[c]	**5g**, *m*-$CHOC_6H_4$	5	**7f**, 60
7	**5h**, *p*-$CH_3OC_6H_4$	13	**7g**, 56
8	**5i**, 1-naphthyl	11	**7h**, 56

[a] Reaction conditions: **5b**−**i** (1.0 equiv), **6** (1.0 equiv). [b] Isolated yield. [c] *i*-Pr_2NH was replaced by Et_3N.

It is worthwhile to note that both the arylboroxine substrate and the diazo substrate in this reaction can bear halide substituents (Table 2, entries 8, 9, and 13; Table 3, entries 3 and 4). To introduce an aryl group bearing halide substituent to the α-position of carbonyl group would be difficult with the Pd-catalyzed reaction due to the anticipated side reactions.

The scope of this α-arylation approach was further explored by using cyclic α-diazocarbonyl substrates (eqs 2 and 3). The reaction with cyclic α-diazoketone **8** and cyclic α-diazo amide **9** under the same conditions provided the corresponding α-arylation products in moderate yields.



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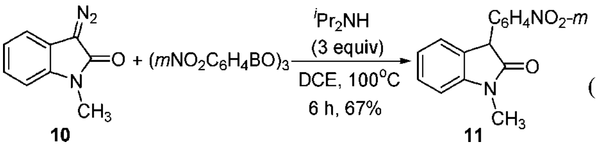
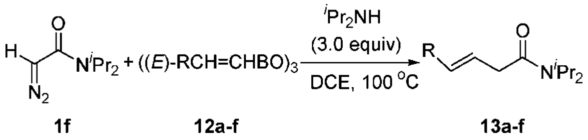


(3)

Compared with α-arylation, α-vinylation of carbonyl compounds has only been sparsely reported.[2d,12] Encouraged by the success of the α-arylation with arylboroxines, we turned our attention to investigate the corresponding α-vinylation by using vinylboroxine. With α-diazo amide **1f**, vinylboroxines **12a**−**f** were applied to the similar reaction conditions, and the results are summarized in Table 4. In all cases, the reaction occurred smoothly, giving α-vinylation products in moderate to good yields. The byproduct attributed from the shift of the double bond to the α,*β* position were not detected in these cases. The same α-vinylation reaction has also been tested with diazo ester **1a**. In that case, the major product of *β*,*γ*-unsaturated ester was accompanied by small amount of α,*β* unsaturated ester as minor product.

Table 4. Reaction of Vinylboroxines **12a**−**f** with **1f**[a]

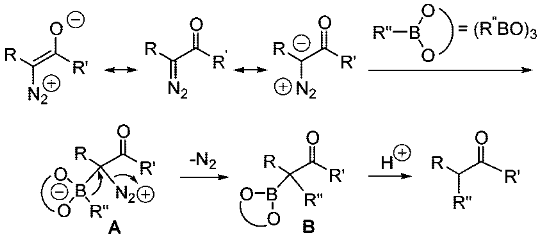


entry	**12**, R	time (h)	yield (**13**, %)[b]
1	**12a**, C_6H_5	12	**13a**, 65
2	**12b**, *p*-$CH_3C_6H_4$	11	**13b**, 88
3	**12c**, *p*-ClC_6H_4	10	**13c**, 77
4	**12d**, 1-naphthyl	13	**13d**, 74
5	**12e**, *n*-pentyl	24	**13e**, 45
6	**12f**, $BnOCH_2CH_2-$	22	**13f**, 61

[a] Reaction conditions: **1f** (1 equiv), **12a**−**f** (1 equiv). [b] Isolated yield.

The mechanism of this α-arylation and α-vinylation is thought to be similar to the reaction of α-diazo compounds with alkylborane (Scheme 2).[3,4] The reaction is initiated by nucleophilic attack of the diazo carbon to boroxine, generating intermediate **A**, followed by 1,2-migration of R″ from boron to carbon to give **B**. Hydrolysis of **B** leads to the product. The additive of diisopropylamine has been found to significantly improve the yield of the reaction. It was observed that adding diisopropylamine could markedly slow down the reaction. Since diazo compounds are generally sensitive to acids, we speculate that the role of diisopropylamine is to neutralize the reaction system by interact with boroxine or acidic species generated during the reactions, thus preventing the diazo substrate from decomposition.

Scheme 2. Mechanistic Rationale



In summary, we have developed a general approach for α-arylation and α-vinylation by the reaction of α-diazocarbonyl compounds with boroxines. Since the reaction conditions are mild and both diazo compounds and boroxines are easily available, this reaction should find an application in organic synthesis.

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Supporting Information Available: Experiment procedure, characterization data, ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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