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Catalytic S_N2'-Selective Substitution of Allylic Chlorides With Arylboronic Esters

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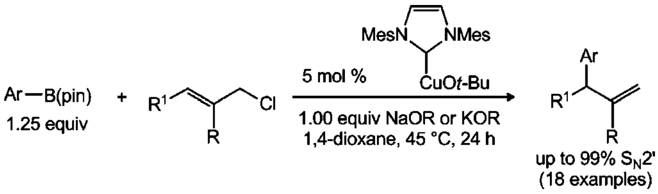
ABSTRACT



A copper-catalyzed S_N2'-selective arylation of allylic chlorides has been achieved using arylboronic esters as nucleophiles. Arylation products were obtained in high yield with a variety of allylic chlorides and arylboronic esters in the presence of a wide range of functional groups. A mechanism is proposed on the basis of the results of stoichiometric experiments and the isolation of the proposed intermediate.

Since its discovery in 1969,[1] the copper-catalyzed allylic alkylation has been a subject of intense study and as a result has been developed into a valuable tool for organic synthesis. With a broad range of substrates, highly efficient S_N2'-selective formation of a new carbon−carbon bond can be achieved, while a number of variants allow enantioselective formation of both tertiary and quaternary stereocenters.[2] In contrast to the large number of reports of copper-catalyzed allylic alkylations, allylic substitutions with sp^2-hybridized carbon nucleophiles remain a formidable challenge. Hoveyda et al. have only recently reported the first general allylic alkenylation.[3] Furthermore, there is still no general S_N2'-selective allylic *arylation*, despite the progress recently made using copper,[4] iridium,[5] and palladium[6] catalysts. The major limitation remains the poor regioselectivity in reactions of primary electrophiles.

In this paper, we report S_N2'-selective allylic arylation of primary allylic electrophiles using a copper(I) catalyst and arylboronic esters as nucleophiles. We also present results of the preliminary study of the reaction mechanism.

One of the major problems in developing a copper-catalyzed S_N2'-selective allylic arylation reaction is the predominant formation of S_N2 products (**3**), generally observed in reactions of primary allylic electrophiles (**1**) (eq 1).[5] It has been proposed that the observed selectivity is a result of the low reactivity of arylcopper complexes, together with the facile formation of more reactive diaryl cuprates (**4**) in the presence of excess aryl nucleophile (**2**).[7] This proposal is supported by the fact that in stoichiometric

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(1) Ronal, P.; Tökes, J. T.; Crabeé, P. *J. Chem. Soc. D* **1969**, *8*, 43–44.

(2) Recent reviews of the copper-catalyzed allylic substitution reactions: (a) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796–823. (b) Falciola, C. A.; Alexakis, A. *Eur. J. Org. Chem.* **2008**, 3765–3780.

(3) Lee, Y.; Akiyama, K.; Gillingham, D. G.; Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 446–447.

(4) (a) Kacprzynski, M. A.; May, T. L.; Kazane, S. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 4554–4558. (b) Selim, K.; Yamada, K.; Tomioka, K. *Chem. Commun.* **2008**, 5140–5142. (c) Selim, K. B.; Matsumoto, Y.; Yamada, K.; Tomioka, K. *Angew.Chem., Int. Ed.* **2009**, *48*, 8733–8735. (d) Ohmiya, H.; Yokobori, U.; Makida, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 2895–2897. (e) Ohmiya, H.; Yokokawa, N.; Sawamura, M. *Org. Lett.* **2010**, *12*, 2438–2440. (f) Piarulli, U.; Daubos, P.; Claverie, C.; Roux, M.; Gennari, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 234–236. (g) Demel, P.; Keller, M.; Breit, B. *Chem.−Eur. J.* **2006**, *12*, 6669–6683.

(5) Polet, D.; Rathgeb, X.; Falciola, C. A.; Langlois, J. B.; El Hajjaji, S.; Alexakis, A. *Chem.−Eur. J.* **2009**, *15*, 1205–1216.

(6) Ohmiya, H.; Makida, Y.; Li, D.; Tanabe, M.; Sawamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 17276–17277.

(7) (a) Bäckvall, J. E.; Sellen, M.; Grant, B. *J. Am. Chem. Soc.* **1990**, *112*, 6615–6621. (b) Bäckvall, J. E.; Persson, E. S.; Bombrun, A. *J. Org. Chem.* **1994**, *59*, 4126–4130.

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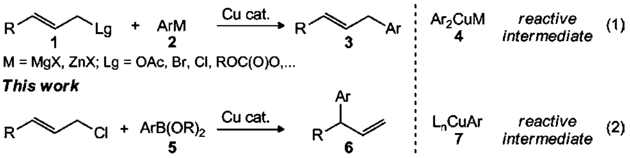
reactions arylcopper complexes (**7**) provide a substitution product with a high S_N2' selectivity, while the preformed diaryl cuprates provide a mixture of products.[7,8]

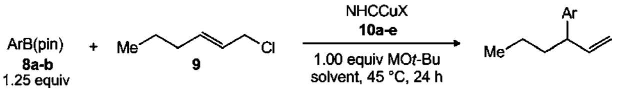
We reasoned that the formation of diaryl cuprates could be prevented if less reactive arylboronic esters were used as nucleophiles (eq 2). This approach is particularly appealing considering the availability, stability, and excellent functional group compatibility of arylboronic esters.[9] Furthermore, when we started the project there were no examples of organoboron compounds being used in copper-catalyzed allylic alkylation or arylation reactions.[10,11]



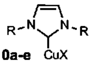
In preliminary screening experiments, we discovered that the S_N2'-selective addition of **8a** to 1-chloro-2-hexene (**9**) can be achieved using copper(I) complexes **10a**–**d** as catalysts in the presence of a stoichiometric amount of KO-*t*-Bu. The best S_N2' selectivity[12] was obtained with **10a**, while catalysts **10b**–**d** provided a higher rate[13] and lower selectivity. Both the alkoxide and the copper catalyst were necessary for an efficient reaction.[14] Interestingly, allylic arylation of **9** with phenyl Grignard and **10a** as a catalyst resulted in exclusive formation of the product of S_N2 reaction, in agreement with previously published results.[15]

In the process of reaction optimization, we discovered that the highest selectivity is obtained with readily available **10e**[16] as a catalyst in 1,4-dioxane (Table 1, entry 5).[13,17] Among the alkali *tert*-butoxides, potassium alkoxide provided the highest yield. With electron-poor boronic esters, such as **8b**, both sodium and potassium alkoxides could be successfully used, with slightly better selectivity obtained with sodium alkoxide[18] (Table 1, entries 9 and 10). Overall, the best results were obtained using reaction conditions described in entry 8 for electron-rich boronic esters and in entry 10 for electron-poor boronic esters.

Table 1. Reaction Optimization



entry	Ar[a]	cat.	mol %	MOt-Bu	solvent	S_N2':S_N2[b]	yield (%)[b]
1	8a	10a	10	KO*t*-Bu	THF	20:1	99
2	8a	10b	10	KO*t*-Bu	THF	8:1	99
3	8a	10c	10	KO*t*-Bu	THF	8:1	99
4	8a	10d	10	KO*t*-Bu	THF	3:1	94
5	8a	10e	10	KO*t*-Bu	1,4-dioxane	42:1	92
6	8a	10e	10	NaO*t*-Bu	1,4-dioxane	50:1	30
7	8a	10e	10	LiO*t*-Bu	1,4-dioxane	35:1	6
8	8a	10e	5	KO*t*-Bu	1,4-dioxane	48:1	98
9	8b	10e	5	KO*t*-Bu	1,4-dioxane	18:1	91
10	8b	10e	5	NaO*t*-Bu	1,4-dioxane	20:1	95



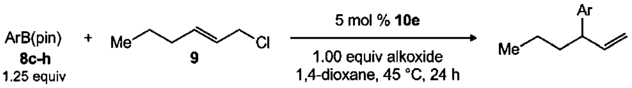
10a-e

10a X = Cl, R = 2,4,6-$Me_3C_6H_4$
10b X = Cl, R = Me
10c X = Cl, R = cyclohexyl
10d X = Cl, R = adamantyl
10e X = O*t*-Bu, R = 2,4,6-$Me_3C_6H_4$

[a] **8a**, Ar = 4-MePh; **8b**, Ar = 4-(CHO)Ph; B(pin) = pinacol boron. [b] Determined by GC analysis.

With the optimized reaction conditions in hand, we explored the reactivity of various arylboronic esters. The reaction can be successfully performed in the presence of a variety of functional groups, including formyl and nitro groups, which are not compatible with previously described copper-catalyzed allylic substitution reactions (Table 2). Furthermore, we observed a direct correlation between the electron-donating ability of the aryl substituents and the regioselectivity. Steric properties of the boronic ester, on the other hand, had little effect on the reaction outcome, as demonstrated by the reaction of the ortho,ortho-disubstituted arylboronic ester **8h**.

Table 2. Arylboronic Esters in Allylic Arylation Reaction



entry[a]	Ar	alkoxide	S_N2'/S_N2[b]	yield[c] (%)
1	4-MeOPh (**8c**)	KO-*t*-Bu	58:1	85
2	4-(CHO)Ph (**8b**)	NaO-*t*-Pent	20:1	97
3	4-CF_3Ph (**8d**)	NaO-*t*-Pent	24:1	75
4	4-NO_2Ph (**8e**)	NaO-*t*-Pent	13:1	92
5	3-NO_2Ph (**8f**)	NaO-*t*-Pent	10:1	66
6	4-BrPh (**8g**)	KO-*t*-Bu	32:1	78
7	2,6-Me_2Ph (**8h**)	KO-*t*-Bu	24:1	85

[a] All reactions were performed on 0.5 mmol scale. [b] Determined by GC analysis. [c] Yield of isolated products.

The scope of the allylic arylation was further explored in reactions of a variety of allylic chlorides. It was discovered that both *E*- and *Z*-substituted electrophiles can be used in the reaction with similar success (Table 3, entries 1 and 2). Azides, nitriles, chlorides, and TBS-protected alcohols are all compatible with the reaction conditions, further demonstrating the exceptional functional group tolerance of the

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(8) For a recent theoretical study, see: Yoshikai, N.; Zhang, S.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 12862–12863.

(9) Hall, D. G. *Boronic Acids*; Wiley-VCH: Weinheim, 2005.

(10) For an early report of a stoichiometric reaction using trialkylborates, see: Miyaura, N.; Itoh, M.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2199–2200.

(11) See ref 4d,e for two recent reports.

(12) Reaction of **8a** and 3-chloro-1-butene under the same reaction conditions afforded S_N2' product as the exclusive product of the reaction.

(13) See the Supporting Information for details.

(14) In the absence of base with **10e** as the catalyst, product was obtained in 8% yield, while in the absence of catalyst the yield was less than 5%.

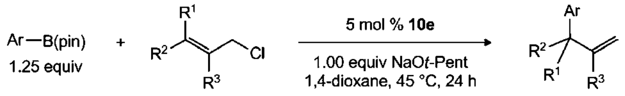
(15) Tominaga, S.; Oi, Y.; Kato, T.; An, D. K.; Okamoto, S. *Tetrahedron Lett.* **2004**, *45*, 5585–5588.

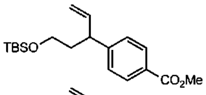
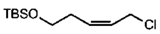
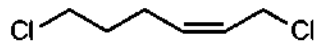
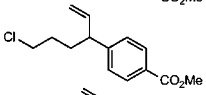
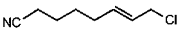
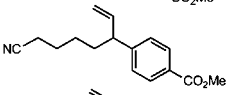
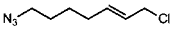
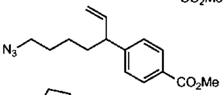
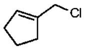
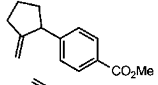
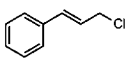
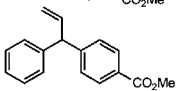
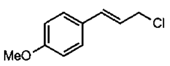
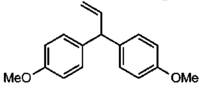
(16) Compound **10e** is prepared in one step from the commercially available IMes·HCl. See the Supporting Information for details.

(17) Addition of water was not beneficial as in the copper-catalyzed arylation of internal alkenes with aryboronic esters, recently reported by Sawamura (ref 4e).

(18) Sodium *tert*-pentoxide and sodium *tert*-butoxide provide the same result.

Table 3. Allylic Chlorides in Allylic Arylation Reaction

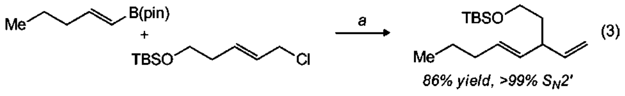


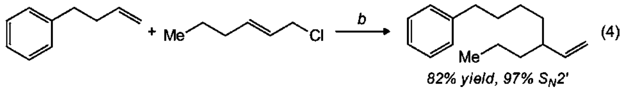
entry[a]	electrophile	product	S_N2':S_N2[b]	yield (%)[c]
1			32:1	91
2			21:1	94
3			20:1	90
4			21:1	92
5			33:1	90
6			30:1	64
7			17:1	90
8[d]			15:1	85

[a] All reactions were performed on 0.5 mmol scale. [b] Determined by GC analysis of pure products. [c] Yield of isolated products. [d] KO-*t*-Bu was used.

reaction. Finally, cyclic and aryl-substituted allylic chlorides are also suitable substrates for allylic arylation (entries 6−8).

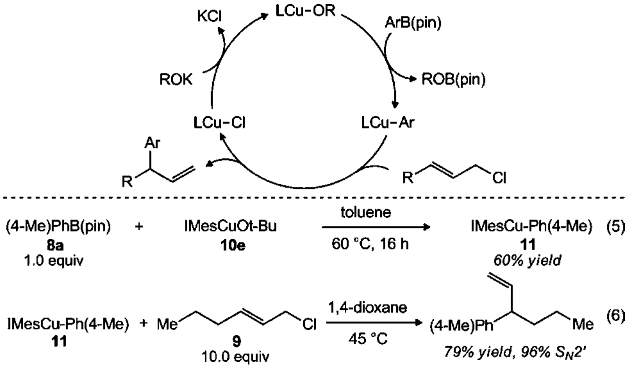
In addition to allylic arylation, we discovered that organoboron reagents can also be used as nucleophiles in copper-catalyzed alkenylation and alkylation of primary allylic electrophiles. With pentenyl boronic ester, the alkenylation product is obtained in good yield and excellent selectivity (eq 3). Allylic alkylation, on the other hand, can be accomplished using trialkylboranes formed in situ from an alkene and 9-BBN (eq 4). The hydroboration−allylic alkylation sequence allows highly efficient and selective one-pot coupling of terminal alkenes and allylic chlorides.





In an attempt to provide a better understanding of the source of the observed S_N2' selectivity, we studied the mechanism of the reaction, with the catalytic cycle presented in Scheme 1 as a working hypothesis. We were able to isolate the product of transmetalation (**11**) from a stoichiometric reaction of **10e** and **8a** (Scheme 1, eq 5) and provide direct evidence for the transmetalation from boron to copper(I).[19,20] The isolation of **11** also allowed us to investigate the potential role of this complex in the second step of the proposed catalytic cycle.

Scheme 1. Proposed Mechanism and Stoichiometric Reactions



A stoichiometric reaction of **11** and **9** resulted in the formation of the expected product within seconds, in good yield and with selectivity comparable to the selectivity obtained in a catalytic reaction (Scheme 1, eq 6). Furthermore, **11** is a competent catalyst and can be used instead of **10e**. Together, these results support the idea that the arylcopper intermediate is the reactive nucleophile responsible for the selectivity observed in catalytic reactions. Finally, in the last step of the catalytic cycle, copper(I) alkoxide is regenerated from copper(I) chloride and KO-*t*-Bu in a well-precedented transformation.[21]

In conclusion, we have developed the first general S_N2'-selective allylic arylation reaction using a copper(I) catalyst and arylboronic esters as nucleophiles. The reaction has a broad substrate scope and can be performed in the presence of a variety of functional groups including formyl, carbomethoxy, nitrilo, azido, chloro, bromo, and nitro groups.

Acknowledgment. This work was supported by the University of Washington.

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

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[19] Ohishi, T.; Nishiura, M.; Hou, Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 5792–5795.

[20] No attempt was made to optimize the reactions conditions used in preparation of **11**.

[21] Mankad, N. P.; Laitar, D. S.; Sadighi, J. P. *Organometallics* **2004**, *23*, 3369–3371.