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Palladium-Catalyzed Conjugate Allylation Reactions of α,β-Unsaturated *N*-Acylpyrroles

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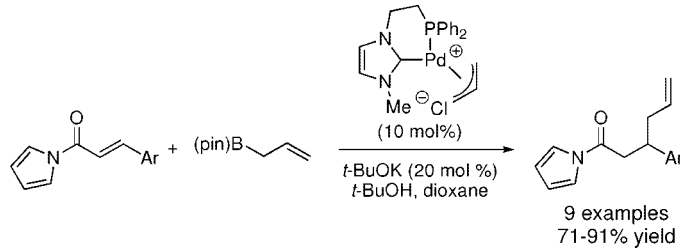
ABSTRACT



Conjugate allylation reactions of α,β-unsaturated *N*-acylpyrroles using allylboronic ester are catalyzed by a palladium complex that is ligated by a bidentate N-heterocyclic carbene. A variety of functional groups are tolerated, and substrates functionalized with electron-withdrawing groups react to afford the highest yields of products. Regioselectivity for 1,4-allylation over 1,2-allylation is demonstrated, and mechanistic experiments are consistent with formation of nucleophilic allylpalladium intermediates.

Conjugate additions of carbon-based nucleophiles to enoate derivatives are important methods for organic synthesis. Although excellent methods exist for the transition-metal-catalyzed addition of certain aryl and alkyl substituents,[1] relatively few catalytic methods have been described for conjugate allylation reactions.[2,3] Several metal-catalyzed allylation reactions of enones afford products resulting from regioselective 1,2-addition of the allylic nucleophile.[4] In significant advances, Morken and co-workers have recently reported enantioselective Ni- and Pd-catalyzed conjugate allylation reactions of dialkylidene ketones such as dibenzylidene acetone,[5] and Snapper and co-workers have reported enantioselective copper-catalyzed Hosomi−Sakurai allylations of cyclic ketoesters.[6] Catalyst-controlled regioselective 1,4-addition reactions of simple enones and enoate derivatives, however, are not currently available.

To address this unmet need, we undertook development of a method for conjugate allylation reactions of α,β-unsaturated *N*-acylpyrroles, practical substrates for conjugate

(1) For a recent review, see: Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, *9*, 1279–1300.

(2) Conjugate allylation reactions using stoichiometric organometallic compounds. Allylsilane: (a) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673–1675. (b) Majetich, G.; Casares, A. M.; Chapman, D.; Behnke, M. *Tetrahedron Lett.* **1983**, *24*, 1909–1912. Allylcopper: (c) Lipshutz, B. H.; Hackmann, C. *J. Org. Chem.* **1994**, *59*, 7437–7477. Allylstannane: (d) Williams, D. R.; Mullins, R. J.; Miller, N. *J. Chem. Soc., Chem. Commun.* **2003**, 2220–2221. Allylbarium: (e) Yanagisawa, A.; Habaue, S.; Yasue, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 6130–6141. Allyltantalum: (f) Shibata, I.; Kano, T.; Kanazawa, N.; Fukuoka, S.; Baba, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1389–1392.

(3) Stereoselective additions of chiral allyl and crotyl phosphonamides: (a) Hanessian, S.; Gomtsyan, A.; Payne, A.; Hervé, Y.; Beaudoin, S. *J. Org. Chem.* **1993**, *58*, 5032–5034. (b) Hanessian, S.; Gomtsyan, A. *Tetrahedron Lett.* **1994**, *35*, 7509–7512. (c) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161–3195.

(4) Representative catalytic enantioselective 1,2-allylation reactions of enones, catalyzed byCuCl: (a) Yamasaki, S.; Fujii, K.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 6536–6537. CuF_2: (b) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910–8911. AgF: (c) Wadamoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 14556–14557.

(5) (a) Sieber, J. D.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 2214–2215. (b) Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 4978–4983.

(6) Shizuka, M.; Snapper, M. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 5049–5051.

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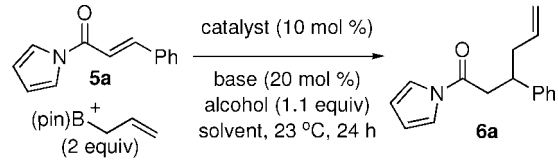
Table 1. Palladium-Catalyzed Allylation of *N*-Acylpyrrole **5a**[a]



entry	catalyst	base	alcohol	solvent	yield (%)[b]
1	none	*t*-BuOK	*t*-BuOH	CH_2Cl_2	<5
2	**1**	*t*-BuOK	*t*-BuOH	CH_2Cl_2	<5
3	**2**	*t*-BuOK	*t*-BuOH	CH_2Cl_2	7[c]
4	**3**	*t*-BuOK	*t*-BuOH	CH_2Cl_2	24[c]
5	**4**	*t*-BuOK	*t*-BuOH	CH_2Cl_2	<5
6	$PdCl_2(NCPh)_2$, $P(OPh)_3$[d]	*t*-BuOK	*t*-BuOH	dioxane	<5
7	**3**	*t*-BuOK	*t*-BuOH	THF	29[c]
8	**3**	*t*-BuOK	*t*-BuOH	dioxane	46[c]
9	**3**	*t*-BuOK	*tert*-amyl alcohol[e]	dioxane	44[c]
10	**3**	*t*-BuOLi	*tert*-amyl alcohol[e]	dioxane	<10
11	**3**	K_2CO_3	*tert*-amyl alcohol[e]	dioxane	21
12[f]	**3**	*t*-BuOK	*tert*-amyl alcohol[e]	dioxane	71[c]

[a] See the Supporting Information for reaction conditions. [b] Yield of **6a** as determined by ^{1}H NMR spectroscopy using $PhSiMe_3$ as an internal standard. [c] Isolated yield of **6a** after column chromatography. [d] 10 mol % of $PdCl_2(NCPh)_2$ and 30 mol % of phosphite were added. [e] Performed with 3.0 equiv of *tert*-amyl alcohol. [f] Performed with 5.0 equiv of allylB(pin).

addition reactions. *N*-Acylpyrroles are versatile building blocks because, as Weinreb amide equivalents, they undergo facile functionalization to the alcohol, aldehyde/ketone, or acid oxidation states.[7] Further, α,β-unsaturated *N*-acylpyrroles display similar reactivity to α,β-unsaturated ketones[8] and undergo arylation, epoxidation, amination, and cyanation reactions.[9] To the best of our knowledge, however, neither catalytic nor reagent-controlled conjugate allylation reactions of *N*-acylpyrroles have been reported.

We reasoned that allylpalladium complexes **1**−**3** would catalyze allylation reactions of enoate derivatives. Our prior studies have demonstrated that the bidentate N-heterocyclic carbene (NHC) ligands in complexes **1**−**3** impart nucleophilicity to the Pd-bound allyl groups.[10,11] These complexes undergo stoichiometric reactions with aldehydes and catalyze allylstannylation of aldehydes. In contrast, allylpalladium complex **4**, ligated by a monodentate NHC ligand, does not react with aldehydes.

We examined allylation of *N*-acylpyrrole **5a** by the pinacol ester of allylboronic acid using palladium complexes **1**−**4** (Table 1). In the absence of catalyst, no reaction occurs. Catalyst **3**, which is ligated by a bidentate NHC−phosphine, is unique in affording a significant yield of the desired product (entry 4). Other palladium complexes, including complexes **1** and **2**, containing alternative bidentate NHC ligands, afford <10% yield of the desired product.

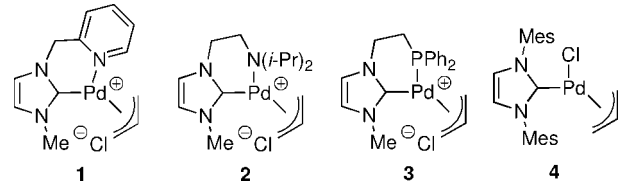


Figure 1. NHC-ligated allylpalladium complexes **1**−**4**.

A screen of solvents and alcohols demonstrated that a combination of dioxane and *tert*-amyl alcohol afforded the highest yield of allylation product **6a**. The use of *tert*-amyl alcohol suppressed formation of ester byproducts resulting from alkoxide attack on the *N*-acylpyrrole.[12] A variety of bases were screened, and potassium *tert*-butoxide gave the highest yields of product. Lithium *tert*-butoxide or an inorganic base such K_2CO_3 or K_3PO_4 had a detrimental effect on the yield. Increasing the quantity of boronic ester to 5 equiv provided the highest yield of product, affording 71% yield of *N*-acylpyrrole **6a**.[13]

(7) (a) Evans, D. A.; Borg, G.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 3188–3191. (b) Lee, S. D.; Brook, M. A.; Chan, T. H. *Tetrahedron Lett.* **1983**, *24*, 1569–1572.

(8) Matsunaga, S.; Kinoshita, T.; Okada, S.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7559–7570.

(9) Arylation: (a) Shintani, R.; Kimura, T.; Hayashi, T. *J. Chem. Soc., Chem. Commun.* **2005**, *321*, 3–3214. (b) Arai, Y.; Kasai, M.; Ueda, K.; Masaki, Y. *Synthesis* **2003**, *151*, 1–1516. Epoxidation: ref 3 and (c) Kinoshita, T.; Okada, S.; Park, R.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4680–4684. Amination: (d) Yamagiwa, N.; Qin, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13419. Cyanation: (e) Mita, T.; Sasaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 514–515.

(10) Barczak, N. T.; Grote, R. E.; Jarvo, E. R. *Organometallics* **2007**, *26*, 4863–4865.

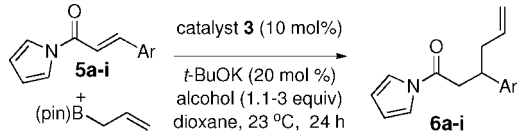
(11) For a recent review of catalysis by nucleophilic allylpalladium complexes, see: Zanoni, G.; Pontiroli, A.; Marchetti, A.; Vidari, G. *Eur. J. Org. Chem.* **2007**, *359*, 9–3611.

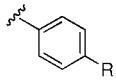
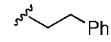
(12) These byproducts were formed in approximately 10% yield when *t*-BuOH was employed. The use of more sterically encumbered alcohols, e.g., trityl alcohol or 1-adamantanol, did not improve the yield further.

A variety of *N*-acylpyrroles with aromatic substituents at the β-position reacted smoothly under these reaction conditions (Table 2). Electron-deficient substrates afforded products in the highest yields, and for these substrates 2 equiv of the allyl boronic ester was sufficient to obtain acceptable yields (cf. entries 2 and 3, 9 and 10). A variety of functional groups, including cyano, carbethoxy, and pyridine, were tolerated (entries 7, 8, and 11). Substrates **5d** and **5g**, containing aryl bromides, underwent facile conjugate addition with no competitive side reactions.[14] *N*-Acylpyrroles with electron-rich aromatic and aliphatic substitutents reacted more slowly and in lower yields.[15] Reactions were generally clean, however, and near-quantitative recovery of unreacted α,β-unsaturated *N*-acylpyrrole was possible. For most substrates, *tert*-amyl alcohol and *t*-BuOH could be used interchangeably (reaction conditions A and B, respectively, Table 2). For certain substrates, however, use of *tert*-amyl alcohol provided a modest increase in yield (cf. entries 4 and 5).

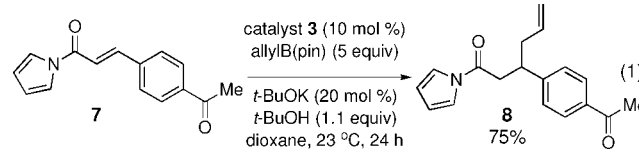
The chemoselectivity of the allylation was examined by subjecting substrate **7**, containing both an α,β-unsaturated *N*-acylpyrrole and a ketone, to our standard reaction conditions (eq 1). Regioselective conjugate addition occurs to afford product **8** in 75% yield. Products resulting from ketone allylation comprised less than 10% of the unpurified reaction mixture.

Table 2. Allylation Reactions of *N*-Acylpyrroles[a]



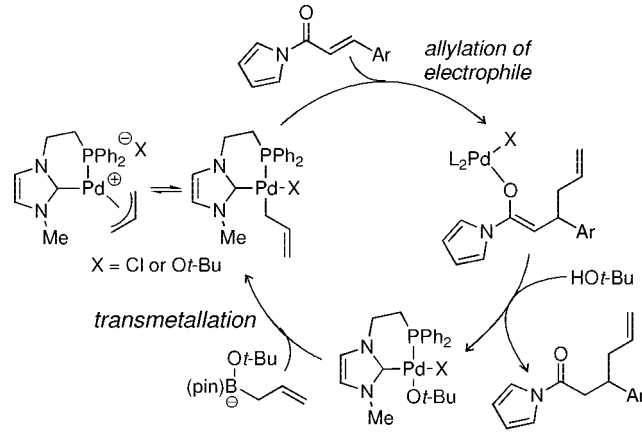
entry	Ar	substrate	product	allylB(pin) equiv	Reaction Conditions	yield (%)[b]
1		**5a**, R = H	**6a**	5	A	71
2		**5b**, R = CF_3	**6b**	2	B	75
3			**6b**	5	B	82
4		**5c**, R = NO_2	**6c**	5	A	89
5			**6c**	5	B	85
6		**5d**, R = Br	**6d**	5	B	77
7		**5e**, R = CN	**6e**	5	B	81
8		**5f**, R = CO_2Me	**6f**	5	A	83
9		**5g**	**6g**	2	B	74
10			**6g**	5	B	91
11		**5h**	**6h**	5	B	83
12		**5i**	**6i**	5	B	<10[c]

[a] Reaction conditions A: *tert*-amyl alcohol (3 equiv). Reaction conditions B: *t*-BuOH (1.1 equiv). See the Supporting Information for full details. [b] Isolated yield after column chromatography. [c] Starting material **5i** was recovered in near-quantitative yield.

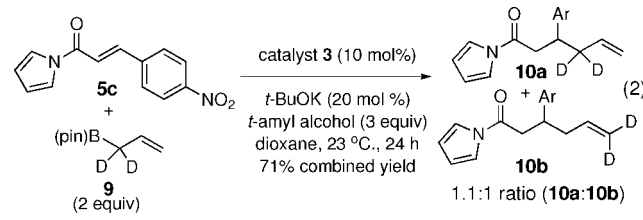


We propose that the mechanism of the reaction proceeds according to the mechanism shown in Scheme 1. The η^1- and η^3-allylpalladium complexes are in equilibrium under the reaction conditions. We hypothesize, based on our prior studies of stoichiometric allylation reactions, that the η^1-allylpalladium complex attacks the *N*-acylpyrrole to initiate the catalytic cycle.[10] The palladium-bound enolate may be protonated by *tert*-butyl alcohol to generate a palladium alkoxide. The catalyst is subsequently regenerated by transmetalation, in analogy to related palladium-catalyzed allylation reactions of imines and aldehydes.[16]

Scheme 1. Proposed Mechanism



To test for this mechanism, we examined the reaction of deuterated allylboronic ester **9**,[17,18] for which equilibration between η^1- and η^3-allylpalladium complexes would scramble the deuterium label (eq 2). Treatment of substrate **5c** with **9** under our reaction conditions afforded a 1.1:1 mixture of products **10a** and **10b**, consistent with the proposed mechanism. An alternative mechanism,[19] involving Lewis acid catalysis by the palladium complex and attack of an



(13) Competitive decomposition pathways consume allylB(pin) to afford, for example, 1,5-hexadiene.

(14) Aryl chlorides and fluorides react to afford products in lower yields, e.g., *p*-chlorophenyl-substituted *N*-acylpyrrole [(2*E*)-3-(4-chlorophenyl)-1-pyrrol-1-yl-2-propene-1-one] affords 32% yield of allylation product under conditions A. The cause of this effect is under investigation.

allylboronate, would be regiospecific, affording only **10b**, and is not consistent with our observations.[20]

We report the palladium-catalyzed conjugate allylation reactions of α,β-unsaturated *N*-acylpyrroles. Several functional groups, including bromo, cyano, pyridyl, and carbonyl groups, are tolerated. Mechanistic experiments are consistent with catalysis by nucleophilic allylpalladium complexes. Current studies include expanding the scope of the reaction, developing an enantioselective variant of the reaction and further mechanistic studies.

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

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(15) For example, *p*-methoxyphenyl-substituted *N*-acylpyrrole [(2*E*)-3-(4-methoxyphenyl)-1-pyrrol-1-yl-2-propene-1-one] affords 13% of allylated product and 80% recovered starting material under reaction conditions A.

(16) (a) Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6641–6647. (b) Solin, N.; Kjellgren, J.; Szabó, K. J. *J. Am. Chem. Soc.* **2004**, *126*, 7026–7033.

(17) Morken and co-workers have demonstrated that Pd-catalyzed allylation of a dialkylidene ketone with **9** provides a single product, due to rapid reductive elimination of a σ-allyl-π-allylpalladium intermediate. See ref 5b.

(18) Palladium-catalyzed crotylation reactions of imines are regioselective and not regiospecific, consistent with rapid isomerization of crotylpalladium intermediates. See: Nakamura, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 2614–2615. Crotylation of acylpyrrole **5c** under our current reaction conditions is prohibitively slow, unfortunately.

(19) Piechaczyk, O.; Cantat, T.; Mézailles, N.; Le Floch, P. *J. Org. Chem.* **2007**, *72*, 4228–4237.

(20) Isomerization of **9** followed by Lewis acid catalysis of allylation has been ruled out by performing the following control experiment: a mixture of **9**, catalyst **3**, *t*-BuOK, and *t*-BuOH in dioxane was monitored by ^{2}H NMR spectroscopy. No isomerization was observed, and **9** decomposes under these conditions.