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Highly regioselective synthesis of substituted tetrahydroquinolines by palladium-catalyzed cyclization of substituted 2-amidophenylmalonates with 1,4-diacetoxybut-2-ene

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ABSTRACT

The reaction of 2-amidophenylmalonates with 1,4-diacetoxybut-2-ene in the presence of a palladium catalyst is described. Substituted tetrahydroquinolines having a vinyl group at the 3- or 2-position were synthesized, in which the regioselectivities of the double allylic substitution reactions have been altered depending on the substituent on the amino group.

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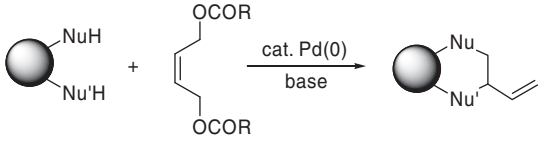
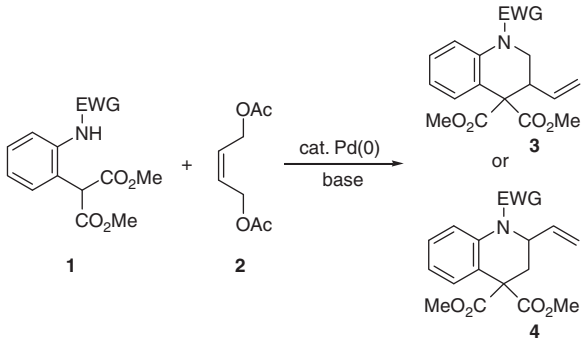
Transition metal-catalyzed nucleophilic allylic substitution reactions have received considerable attention and have been extensively studied due to their versatile and specific reactivities.[1] Among them, 2-butene-1,4-diol derivatives, such as the dicarbonate, are attractive substrates for palladium-catalyzed reactions with nucleophiles. For example, a compound having two nucleophilic moieties within the molecule reacted with 1,4-diacyloxybut-2-ene to afford the cyclized product via successive double allylic substitutions (Scheme 1). Various heterocyclic compounds such as quinoxalines,[2] benzoxazines,[3] piperidines,[4] morpholines,[4,5] benzodioxanes,[6] oxazolidinones,[7] pyrroles,[8] and dihydrofurans[9] have been synthesized by this methodology. In our studies on the palladium-catalyzed cascade cyclizations using compounds containing two nucleophilic moieties,[10] we focused on the nucleophilic activity of 2-amidophenylmalonates toward the 1,4-diacyloxybut-2-ene. By introducing nucleophilic nitrogen and carbon moieties within the molecule, we thought that substituted tetrahydroquinolines, common structures in many biologically active compounds,[11] could be constructed in one step. Herein, we describe the palladium-catalyzed reaction of 2-amidophenylmalonates **1** with 1,4-diacetoxybut-2-ene **2**, in which the substituted tetrahydroquinolines **3** or **4** having a vinyl group at the 3- or 2-position have been regioselectively constructed depending on the substituent on the amino group (Scheme 2).



Scheme 1.



Scheme 2.

Our initial attempts were carried out using 2-(*p*-toluenesulfonylamino)phenylmalonate (**1a**)[12] and (*Z*)-1,4-diacetoxybut-2-ene (**2**).[13] When **1a** and **2** were treated with 5 mol % $Pd_2(dba)_3{\cdot}CHCl_3$, 20 mol % DPPE and ^tBuOK in THF under reflux for 2 h, the 3-vinyltetrahydroquinoline **3a** was obtained in 27% yield (Table 1, entry 1). By changing the base (entries 2–4), the yield of **3a** was improved to 79% with K_2CO_3 (entry 4). After further experimentation with various ligands (entries 5–8), we found that **3a** could be produced in 86% yield when DPPP was used as the ligand (entry 7).

We next attempted the reactions using the 2-amidophenylmalonates **1b–f** having various electron-withdrawing groups on the amino group (Table 2).[14] When the sulfonamide-type substrates **1b** and **1c** having a benzenesulfonyl- and a 2-naphthalenesulfonyl group were subjected to the reactions with **2**, the 3-vinyltetrahydroquinolines **3b** and **3c** were produced in 89% and 55% yield, respectively (entries 1 and 2). On the other hand, it is interesting to note that the 2-vinyltetrahydroquinoline **4d** was produced

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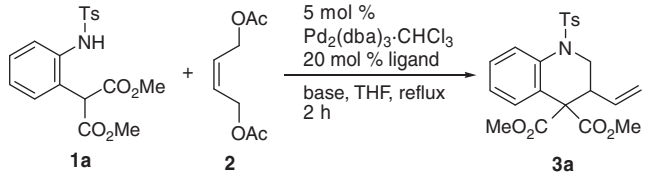
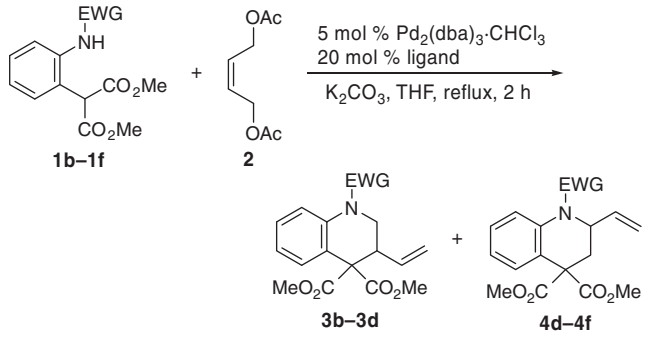
Table 1
Effect of base and ligand



1a 2 3a

Entry	Base	Ligand	Yield of **3a** (%)
1	^{t}BuOK	DPPE	27
2	Et_3N	DPPE	22
3	K_3PO_4	DPPE	58
4	K_2CO_3	DPPE	79
5	K_2CO_3	DPPF	61
6	K_2CO_3	DPPB	68
7	K_2CO_3	DPPP	86
8	K_2CO_3	(±)-BINAP	36

Table 2
Reactions using substrates **1b–f** with **2**



1b–1f 2 3b–3d 4d–4f

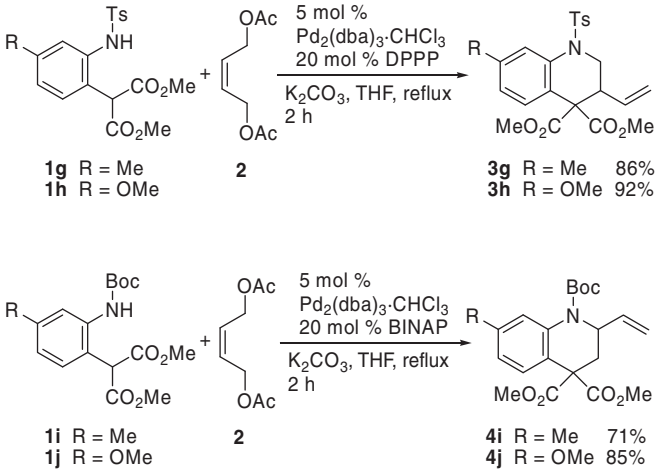
Entry	EWG	Yields (%)	
		3	**4**
1[a]	Benzenesulfonyl (**1b**)	89	–
2[a]	2-Naphthalenesulfonyl (**1c**)	55	–
3[a]	Benzyloxycarbonyl (Cbz) (**1d**)	7	27
4[b]	Benzyloxycarbonyl (Cbz) (**1d**)	14	74
5[b]	Methoxycarbonyl (**1e**)	–	66
6[b]	*t*-Butoxycarbonyl (Boc) (**1f**)	–	82

[a] DPPP was used as the ligand.
[b] (±)-BINAP was used as the ligand.

predominantly when the benzyloxycarbonyl (Cbz)-substituted substrate **1d** was used (entry 3). Although the yield of the resulting **4d** was low (27%), it was dramatically improved to 74% by carrying out the reaction in the presence of (±)-BINAP as the ligand (entry 4). Similar results were obtained in the reactions of other carbamate-type substrates. Thus, compounds **1e** and **1f**, containing a methoxycarbonyl and a *t*-butoxycarbonyl (Boc) group, were regioselectively transformed to the corresponding 2-vinyltetrahydroquinolines **4e** and **4f** in 66% and 82% yield, respectively (entries 5 and 6). From these results, it is now clear that the regiochemical course of the reaction is altered depending on the electron-withdrawing group on the amine.

A plausible mechanism for the cyclization is shown in Scheme 3. On reacting with the palladium catalyst, 1,4-diacetoxybut-2-ene **2** is converted to the π-allylpalladium complex **5**, which is further subjected to the reaction with the 2-amidophenylmalonate **1**. When the sulfonamide-type substrate was used, the corresponding aza-anion **6** was selectively generated because of the strong electron-withdrawing character of the sulfonyl group.[15] As a result, the nucleophilic attack of the sulfonamide initially occurs to afford the intermediate **7**, which further reacts with the malonate moiety in the presence of palladium to produce the 3-vinyltetrahydroquinolines **3** in a regioselective manner. On the other hand, the malonate anion **8** would be predominantly produced in the case of the carbamate-type substrate,[15] which would lead to the formation of the 2-vinyltetrahydroquinolines **4** via the intermediate **9**.[16]

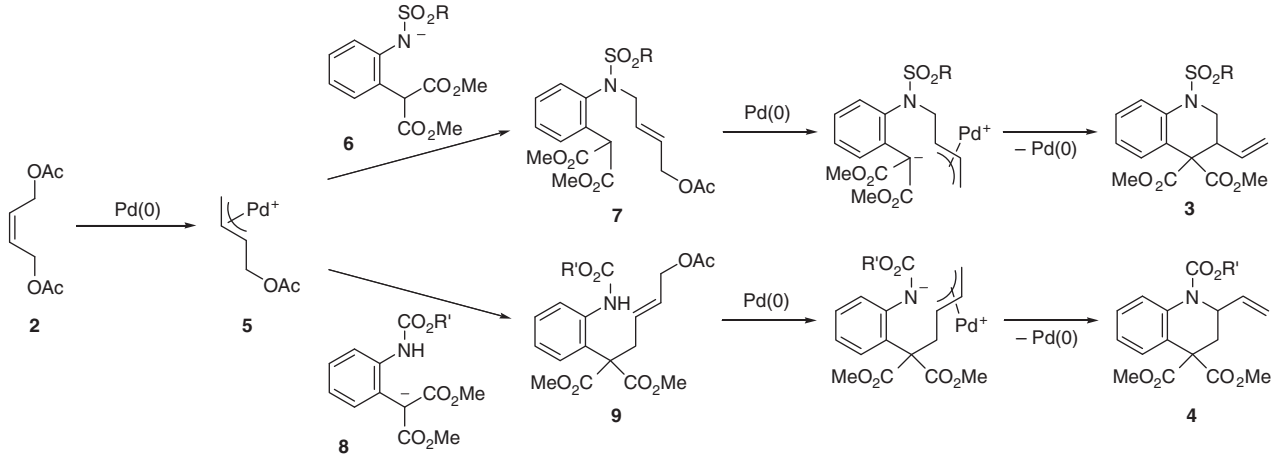
We next carried out a study of the substrate scope. When the tosylamides **1g** and **1h**, containing methyl and methoxy groups on the aromatic ring, were subjected to the reactions with **2**, the



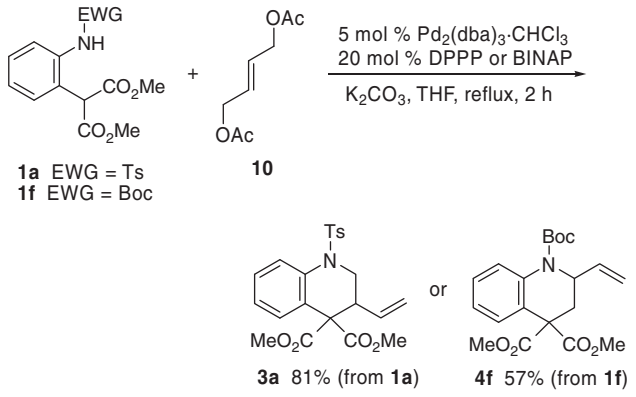
1g R = Me
1h R = OMe
2
3g R = Me 86%
3h R = OMe 92%

1i R = Me
1j R = OMe
2
4i R = Me 71%
4j R = OMe 85%

Scheme 4.



Scheme 3.



Scheme 5.

3-vinyltetrahydroquinolines **3g** and **3h** were produced in 86% and 92% yield, respectively (Scheme 4). Similarly, the reactions of the carbamates **1i** and **1j** bearing methyl and methoxy groups on the aromatic ring also proceeded to give the 2-vinyltetrahydroquinolines **4i** and **4j** in 71% and 85% yield, respectively. When (*E*)-1,4-diacetoxybut-2-ene (**10**) was reacted with the tosylamide **1a** and the *t*-butoxy carbamate **1f**, the corresponding products **3a** and **4f** were obtained in 81% and 57% yield, respectively (Scheme 5). This implies that the reactions occurred via the common π-allylpalladium intermediate **5** regardless of the stereochemistry of the substrate **2**.

In summary, the studies described above have resulted in the regioselective synthesis of vinyltetrahydroquinolines by a palladium-catalyzed cyclization between the 2-amidophenylmalonates and 1,4-diacetoxybut-2-ene. The regioselectivity of the reaction can be altered depending on the substituent on the amino group.

Acknowledgment

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12. The substrate **1a** was prepared from dimethyl (2-nitrophenyl)malonate via hydrogenetion of the nitro group followed by tosylation of the resulting amino moiety. Other substrates **1b**–**j** also were prepared by the similar method.
13. *General procedure for the palladium-catalyzed reaction of 2-amidophenylmalonates with 1,4-diacetoxybut-2-ene*: To a stirred solution of the sulfonamide **1a** (30 mg, 0.079 mmol) and 1,4-diacetoxybut-2-ene **2** (16.4 mg, 0.095 mmol) in THF (2 mL) were added $Pd_2(dba)_3{\cdot}CHCl_3$ (4.1 mg, 3.95 μmol), dppp (6.5 mg, 15.8 μmol), and K_2CO_3 (43.7 mg, 0.318 mmol) at rt, and stirring was continued for 30 min at the same temperature under an argon atmosphere. The reaction mixture was then allowed to heat to 80 °C, and stirred for 2 h. After filtration of the reaction mixture using a small amount of silica gel followed by concentration, the residue was chromatographed on silica gel with hexane/AcOEt (80:20, v/v) as eluent to give the 3-vinyltetrahydroquinoline **3a** (29.3 mg, 86%) as colorless prisms. Compound **3a**: mp 111.7–113.8 °C (AcOEt/Hex/$CHCl_3$);. IR (KBr) 2953, 1746, 1721, 1489, 1361, 1240, 1178, 1099, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 2.98 (dt, *J* = 4.0, 9.0 Hz, 1H), 3.56 (s, 3H), 3.64 (s, 3H), 3.99 (dd, *J* = 9.0, 13.2 Hz, 1H), 4.09 (dd, *J* = 4.0, 13.2 Hz, 1H), 5.10 (dd, *J* = 0.8, 17.2 Hz, 1H), 5.15 (dd, *J* = 0.8, 10.4 Hz, 1H), 5.86 (ddd, *J* = 9.0, 10.4, 17.2 Hz, 1H), 7.09 (dt, *J* = 0.8, 7.8 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.27 (dt, *J* = 1.2, 7.8 Hz, 1H), 7.33 (dd, *J* = 1.2, 7.8 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.82 (dd, *J* = 0.8, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4 (CH_3), 43.0 (CH), 47.6 (CH_2), 52.5 (CH_3), 52.7 (CH_3), 60.8 (Cq), 119.0 (CH_2), 122.6 (CH), 124.0 (CH), 124.5 (Cq), 127.2 (CH), 128.6 (CH), 129.6 (CH), 131.1 (CH), 134.2 (CH), 136.3 (Cq), 136.5 (Cq), 143.8 (Cq), 169.2 (Cq), 169.9 (Cq); HRMS (ESI) *m/z* calcd for $C_{22}H_{24}NO_6S$ [M^++H^+] 430.1324, found 430.1320.
14. By following the same procedure described in ref 13, the 2-vinyltetrahydroquinoline **4f** was prepared from **1f** and **2** in the presence of BINAP in 82% yield as colorless needles: mp 103.9–105.6 °C (AcOEt/Hex/$CHCl_3$); IR (KBr) 2980, 1740, 1694, 1491, 1250, 1160, 1132, 1071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.13 (dd, J = 9.6, 13.6 Hz, 1H), 2.99 (dd, *J* = 8.0, 13.6 Hz, 1H), 3.68 (s, 3H), 3.87 (s, 3H), 4.86 (tddd, *J* = 1.2, 6.4, 8.0, 9.6 Hz, 1H), 5.07 (td, *J* = 1.2, 10.4 Hz, 1H), 5.17 (td, *J* = 1.2, 17.2 Hz, 1H), 5.68 (ddd, *J* = 6.4, 10.4, 17.2 Hz, 1H), 7.04 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.10 (dt, *J* = 1.6, 7.6 Hz, 1H), 7.29 (dt, *J* = 0.8, 7.6 Hz, 1H), 7.49 (dd, *J* = 0.8, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2 (CH_3), 38.8 (CH_2), 53.00 (CH_3), 53.03 (CH_3), 53.2 (CH), 57.8 (Cq), 81.0 (Cq), 115.1 (CH_2), 124.4 (CH), 125.4 (CH), 126.8 (CH), 127.9 (CH), 131.3 (Cq), 136.4 (Cq), 137.4 (CH), 153.3 (Cq), 170.1 (Cq), 170.3 (Cq); HRMS (ESI) *m/z* calcd for $C_{20}H_{25}NO_6Na$ [M^++Na^+] 398.1580, found 398.1582.
15. The pK_a values of the tosylamide and the malonate moiety in **1a**, using the ChemAxon's pKa calculation method are 7.37 and 10.17, respectively. On the other hand, the pK_a value of the *tert*-butoxycarbamate group in **1f** is 11.68.
16. For examples showing the difference in reactivity between sulfonamides and carbamates, see: (a) Ishikawa, T.; Aikawa, T.; Watanabe, S.; Saito, S. *Org. Lett.* **2006**, *8*, 3881; (b) Chataingner, I.; Panel, C.; Gérard, H.; Piettre, S. R. *Chem. Commun.* **2007**, 3288.