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Palladium-Catalyzed Cross-Coupling of Unactivated Alkenes with Acrylates: Application to the Synthesis of the C13–C21 Fragment of Palmerolide A

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Functionalized butadienes are ubiquitous structural motifs in natural products, and they are also useful building blocks in modern organic synthesis.[1] The construction of butadiene scaffolds is frequently accomplished using the Horner–Wadsworth–Emmons olefination reaction.[2] In recent years, with the development of transition-metal-catalyzed coupling reactions, butadiene synthesis that involves the use of either palladium,[3] rhodium,[4] or ruthenium[5] complexes as catalysts have been reported. However, for these reactions, the need for prefunctionalizing the reactants and the undesired formation of stoichiometric amounts of waste make them neither atom economical nor environmentally benign.[6] Consequently, the establishment of catalytic reactions that involve the formation of a C_{sp^2}–C_{sp^2} bond between two olefin substrates through direct C−H bond functionalization, thus giving butadienes, are necessary. Pioneering work on stoichiometric palladium-mediated oxidative coupling of arenes with electron-deficient olefins, as well as a catalytic variant thereof, was first reported by the research group of Fujiwara.[7] Building on those results, palladium-catalyzed direct C−H bond functionalization reactions are now employed in the synthesis of complex organic molecules.[8] To date, despite the efficiency of direct (hetero)aryl C−H bond functionalization reactions,[9] direct alkene–alkene coupling reactions involving alkenyl C−H bond activation are rarely reported. This paucity is primarily due to the inertness of the C−H bond in simple olefins, and the difficulties in promoting the desired cross-coupling while avoiding homocoupling.[10] To date, a number of successful examples of such cross-coupling reactions have been reported. Ishii and coworkers reported the cross-coupling reaction of vinyl carboxylates with acrylates as catalyzed by Pd^{II} with vanadomolybdophosphoric acid.[11] Yu and co-workers reported cross-coupling reactions of activated alkenes and functionalized 1,3-butadiene.[12] A rhodium-catalyzed oxidative C−H olefination of functionalized alkenes was also developed by Glorious and co-workers.[13] Despite the success in our initial report on the palladium-catalyzed cross-coupling of two olefins to form dienes, the reaction of more elaborate aliphatic olefins did not afford the desired products.[14] Thus as part of an effort to synthesize the natural product, palmerolide A, which contains a complex diene motif, we needed to find reaction conditions that would allow alkyl-substituted alkenes to couple with acrylates. Accordingly, we report herein a new method for the coupling of alkyl-substituted alkenes with acrylates along with its application toward the synthesis of the C13–C21 fragment of palmerolide A.

Initially, using our previously reported reaction conditions, the model reaction of **1a** (1 equivalent) with *n*-butyl acrylate (2 equivalent) did not afford any desired product.[14] To obtain the product, different bidentate ligands were used to increase the catalytic activity of the palladium catalyst (Table 1, entries 1–4). The results showed that, among the ligand tested, 1,10-phenanthroline was the most efficient in promoting the cross-coupling reaction (Table 1, entry 4). Unfortunately, the reaction was not selective, the *E* and *Z* products being obtained in equal amounts (50:50). To increase the selectivity, a series of protected homoallylic alcohols were employed. To our delight, with the TIPS-protected substrate, the *E* and *Z* isomers were obtained in a ratio of 75:25, albeit the reaction yield was low (Table 1, entry 9) To further improve the reaction yield and stereoselectivity, the catalyst loading, temperature, and choice of solvent were varied. Ultimately, we found that the following reaction conditions were the most effective: 10 mol % $Pd(OAc)_2$, 12 mol % 1,10-phenanthroline, 12 mol % $AgSbF_6$ as an additive, and 2 equivalents of $Cu(OAc)_2$ as an oxidant in NMP/PivOH (v/v, 1:1) at 120 °C for 24 hours. When using these reaction conditions, the desired coupling product was obtained in 82 % yield with an *E*/*Z* ratio of 75:25 (Table 1, entry 17). Moreover, the ^{1}H NMR analysis of the crude reaction mixture indicated that neither products derived from a homocoupling reaction of alcohol **1a** nor those derived from the dimerization of butyl acrylate **2** were observed under the optimized reaction conditions. Other oxidants, such as AgOAc, Ag_2O, and benzoquinone, gave relatively poor yields of the cross-coupling product.

With optimized coupling reaction conditions established, we expanded the scope of the reaction by examining the cross-coupling between a dozen structurally diverse TIPS-

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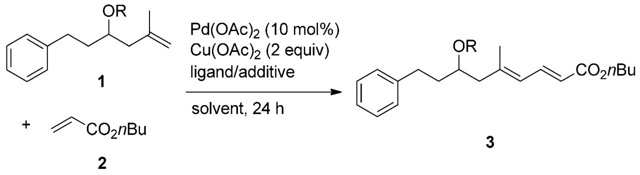
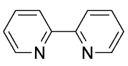
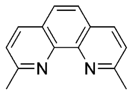
Table 1. Optimization of reaction conditions for the direct cross-coupling between olefins.[a]



Entry	R	Ligand/ additive	*T* [°C]	Solvent (1:1)	Yield [%]	*E*/*Z* [%][b]
1	H	**L1**	60	DMSO/ AcOH	23	50:50
2	H	**L2**	60	DMSO/ AcOH	–	–
3	H	**L3**	60	DMSO/ AcOH	–	–
4	H	**L4**	60	DMSO/ AcOH	32	50:50
5	Ac	**L4**	60	DMSO/ AcOH	12	50:50
6	Bz	**L4**	60	DMSO/ AcOH	14	50:50
7	Bn	**L4**	60	DMSO/ AcOH	15	55:45
8	TBDPS	**L4**	60	DMSO/ AcOH	11	55:45
9	TIPS	**L4**	60	DMSO/ AcOH	14	75:25
10	TIPS	**L4**	90	DMSO/ PivOH	23	75:25
11	TIPS	**L4**	90	NMP/PivOH	34	75:25
12	TIPS	**L4**	120	NMP/PivOH	65	75:25
13	TIPS	**L4**	130	NMP/PivOH	60	75:25
14	TIPS	**L4**/$AgBF_4$	120	NMP/PivOH	68	75:25
15	TIPS	**L4**/ AgOTf	120	NMP/PivOH	62	75:25
16	TIPS	**L4**/ $AgClO_4$	120	NMP/PivOH	59	75:25
17	TIPS	**L4**/ $AgSbF_6$	120	NMP/PivOH	82	75:25

[a] The reaction conditions are as follows: olefin **1** (0.3 mmol), *n*-butyl acrylate (0.6 mmol), $Pd(OAc)_2$ (10 mol%), ligand (12 mol%), and silver salt (12 mol%) in mixed solvent at the indicated temperature. [b] The configuration of the product was confirmed by NMR spectroscopy after purification. Bn = benzyl, Bz = benzoyl, DMSO = dimethylsulfoxide, NMP = *N*-methyl-2-pyrrolidinone, Piv = pivalyl, TBDMS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.


L1
2,2'-bipyridine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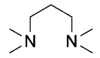
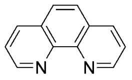
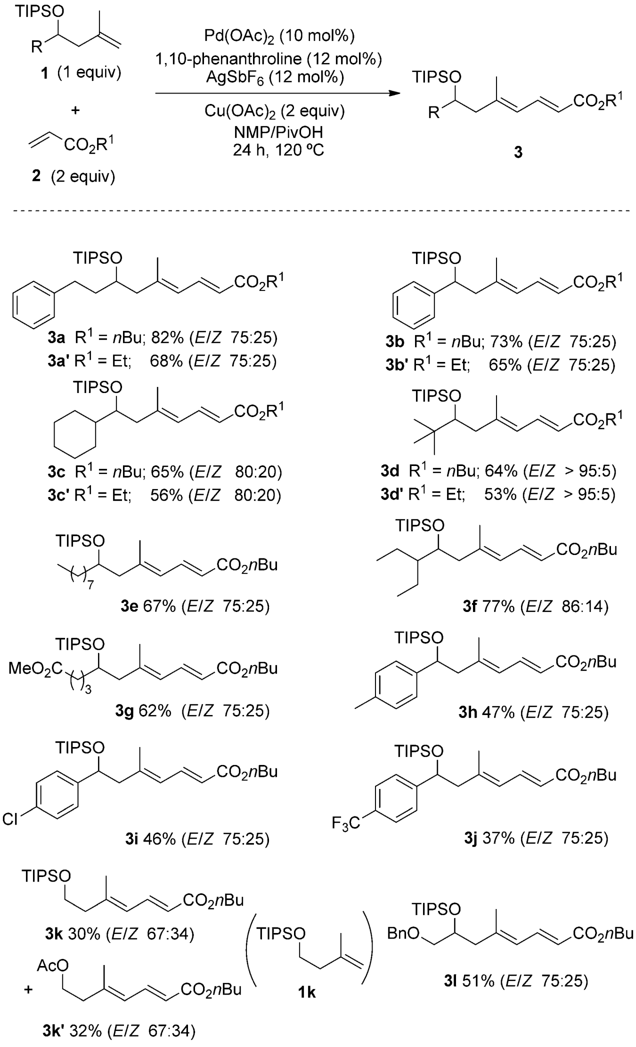

L3
N^1,N^1,N^3,N^3-tetramethylpropane-1,3-diamine

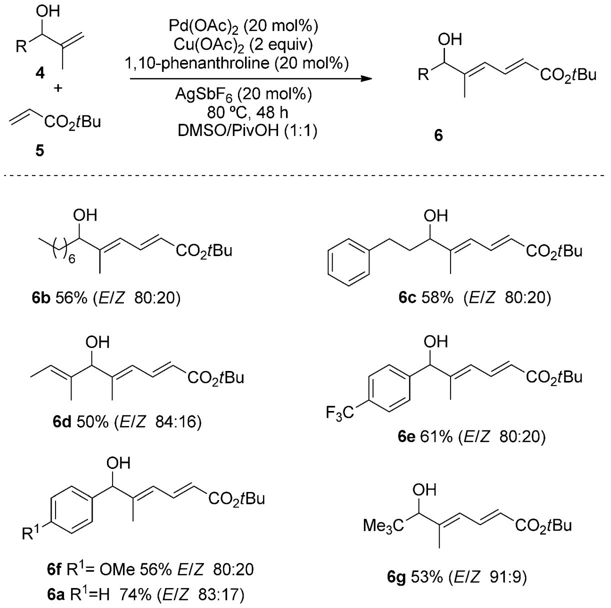

L4
1,10-phenanthroline



Scheme 1. Exploration of the scope of the homoallylic alcohol component in the coupling reaction with *n*-butyl acrylate. The reactions were carried out as follows: olefin **1** (0.3 mmol), *n*-butyl acrylate (0.6 mmol), $Pd(OAc)_2$ (10 mol%), 1,10-phenanthroline (12 mol%), $Cu(OAc)_2$ (0.6 mmol) and $AgSbF_6$ (12 mol%) in NMP/PivOH (v/v = 1:1) at 120 °C for 24 h. The yields and *E*/*Z* ratios indicated were determined upon isolation.

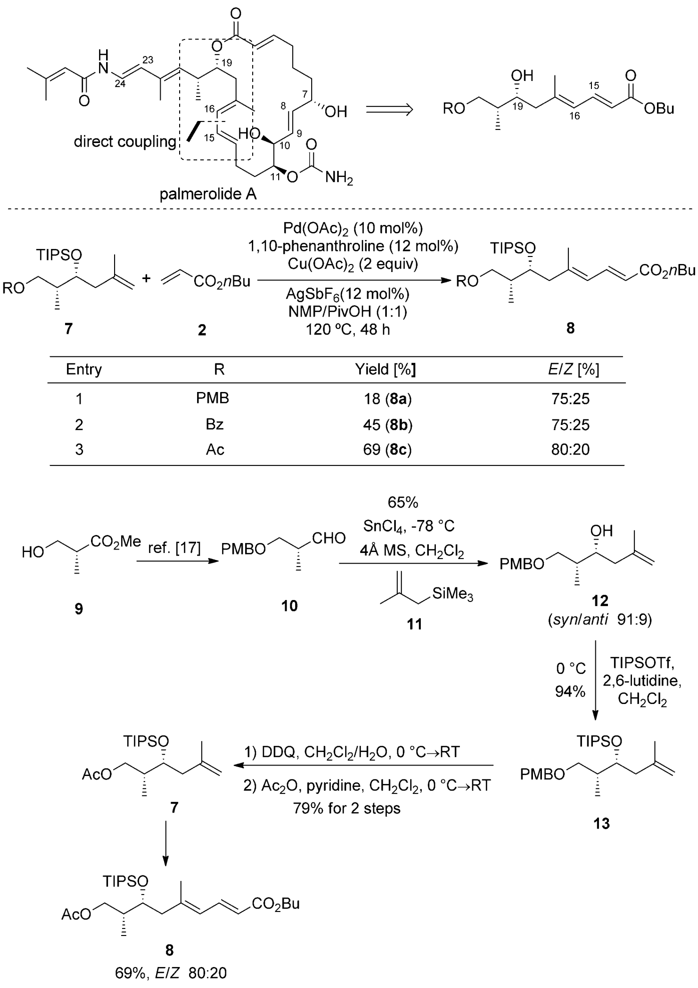
protected homoallylic alcohols and either *n*-butyl acrylate or ethyl acrylate. As shown in Scheme 1, all of the reactions gave the coupling products in moderate to good yields with moderate *E*/*Z* ratios. *n*-Butyl acrylate reacted effectively to give the coupling product in a higher yield than that observed for ethyl acrylate, although there was no improvement in the *E*/*Z* ratio. Also, the reaction could tolerate substrates containing a chlorine atom, such as 4-chlorophenyl substrate **3i**, thus giving access to products that could be synthetically elaborated. Interestingly, the *E*/*Z* isomer ratio was affected by the nature of the substituent on the carbinolic carbon atom of the homoallylic alcohol. For example, when the hydroxylated carbon atom also bears either a phenyl group or a primary alkyl group, *E*/*Z* ratios of 75:25 were observed for the corresponding products (Scheme 1; **3a**, **3a′**, **3b**, **3b′**, **3e**, **3g**, **3h**, **3i**, **3j**, and **3l**). Products with higher *E*/*Z* ratios (80:20 and 86:14) were obtained when using substrates bearing secondary alkyl groups on the carbinolic carbon atom (Scheme 1; **3c**, **3c′**, **3f**). However, when the carbinolic carbon atom of the substrate bears a tertiary alkyl group (Scheme 1; **3d** and **3d′**) the corresponding products were obtained with *E*/*Z* ratios of greater than 95:5, thus suggesting that steric bulk influences the stereochemical outcome of these reactions. We also noticed that when a primary TIPS-protected homoallylic alcohol **1k** was used as the substrate, products **3k** and **3k′** were obtained in comparable yields and with similar levels of stereoselectivity.

In view of the usefulness of dienyl alcohols in organic synthesis,[1]we also investigated the cross-coupling reaction of nonprotected allylic alcohol **4a** with *tert*-butyl acrylate. In the presence of 20 mol % of $Pd(OAc)_2$, 20 mol % 1,10-phenanthroline as a ligand, and 20 mol % $AgSbF_6$ as an additive, diene **6a** was obtained in good yield and stereoselectivity (Scheme 2). Other aryl-, alkyl-, and alkenyl-substituted allylic alcohols also gave the corresponding dienyl alcohols in moderate yield and stereoselectivity (Scheme 2). These results further demonstrate the versatility of our cross-coupling reaction.



Scheme 2. Cross-coupling between nonprotected allylic alcohols and *tert*-butyl acrylate to form dienyl alcohols.

With this efficient protocol in hand, next we focused on applying our methodology to the total synthesis of the natural product, palmerolide A, which was first isolated in 2006.[15] To date, a few total syntheses have been reported by the research group of Nicolaou[16a,b] and those of others.[16c 16d] Our approach to the synthesis of this natural product requires the construction of C13–C21 key fragment **8**, which contains the *E*-dienyl-alcohol structure. We envisioned that diene **8** could be readily accessible using our cross-coupling method. As depicted in Scheme 3, the reaction of readily available intermediate **7** with *n*-butyl acrylate using our optimized reaction conditions afforded the desired diene **8**. Even though the yield was poor for the PMB-protected substrate **7**, the acetyl- and benzoyl-protected derivatives **7** gave significantly better results. In fact, the reaction of acetylated **7** gave the desired diene **8** in moderate yield (69 %) and a respectable 80:20 *E*/*Z* ratio (Scheme 3).



Entry	R	Yield [%]	*E*/*Z* [%]
1	PMB	18 (**8a**)	75:25
2	Bz	45 (**8b**)	75:25
3	Ac	69 (**8c**)	80:20

Scheme 3. Synthesis of the C13–C21 key fragment of palmerolide A. DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone, PMB = *p*-methoxybenzyl, Tf = trifluoromethanesulfonyl.

In conclusion, we have developed a straightforward palladium-catalyzed cross-coupling reaction of either homoallylic or allylic alcohols with acrylates that gives dienyl alcohols in moderate to high yields, and with good stereoselectivity. We have also applied this method to the synthesis of the key C13–C21 fragment of palmerolide A. Further studies towards the synthesis of palmerolide A and other complex natural products are in progress.

Experimental Section

To a 5 mL round-bottomed flask equipped with a magnetic stirring bar was added substituted alkene (0.30 mmol), $Pd(OAc)_2$ (10 mol %, 0.03 mmol), $Cu(OAc)_2$ (0.6 mmol, 2.0 equiv), 1,10-phenanthroline (12 mol %, 0.036 mmol), $AgSbF_6$ (12 mol %, 0.036 mmol), *n*-butyl acrylate (0.6 mmol, 2.0 equiv), and 0.6 mL NMP/PivOH (v/v = 1:1). The reaction mixture was stirred at 120 °C for 24 h. The reaction mixture was cooled to room temperature, followed by the addition of saturated aqueous $NaHCO_3$ and ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtrated, and concentrated in vacuo. The resulting residue was purified using column chromatography on silica gel to give the desired products.

Acknowledgements

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Keywords: butadienes • C–H bond functionalization • cross-coupling • palladium • palmerolide A

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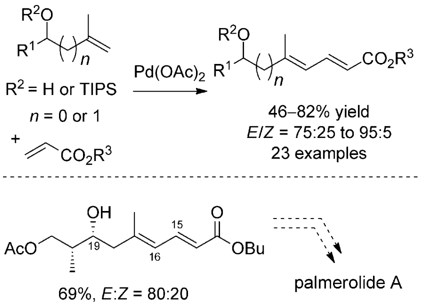
Diene to meet: A palladium-catalyzed cross-coupling reaction between alkyl-substituted olefins and acrylates give the corresponding butadienes in moderate yield and stereoselectivity. This atom-economical reaction, which forms C_{sp^2}–C_{sp^2} bonds, tolerates a wide range of allylic and homoallylic alcohols, and acrylates (see scheme; TIPS = triisopropylsilyl). The methodology was applied to the synthesis of the C13–C21 fragment of palmerolide A.



Cross-Coupling

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