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Palladium-Catalyzed Regio- and Enantioselective Allylic Alkylation of Bis Allylic Carbonates Derived from Morita–Baylis–Hillman Adducts

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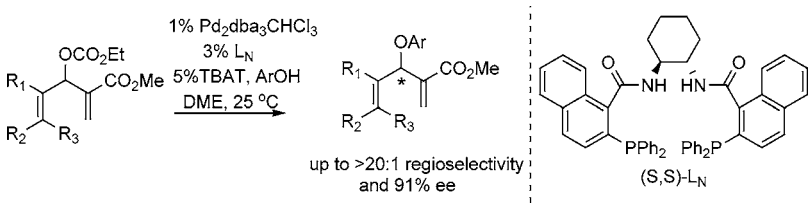
ABSTRACT



Morita–Baylis–Hillman diene adducts are used as substrates in the palladium-catalyzed asymmetric allylic alkylation reaction with oxygen and carbon nucleophiles in good regio- and enantioselectivity.

Palladium-catalyzed asymmetric allylic alkylation (AAA) is a powerful approach for creating stereogenic centers. In the exploration of the scope of this reaction, several "soft" nucleophiles have proven to be proficient.[1] More recently, "hard" nucleophiles, such as ketone and amide enolates and aliphatic alcohols, have had some success.[2] In addition to examining the nucleophilic partner in the palladium AAA reaction, the electrophilic counterpart has also shown its versatility. A few years ago, our group showed that racemic Morita−Baylis−Hillman adducts could function as electrophiles for a dynamic kinetic asymmetric transformation (DYKAT) with phenol nucleophiles.[3] Simple deprotection of the phenol alcohol provided chiral Morita−Baylis−Hillman adducts, synthetically useful building blocks which are the focus of much research.[4] To expand the scope of these electrophiles even further, diene adducts, which result from the Morita−Baylis−Hillman reaction between methyl acrylate and α,β-unsaturated aldehydes, were examined as electrophiles. Besides the obvious goals of obtaining good reactivity and enantioselectivity, getting the desired regioselectivity could potentially be an issue since the introduction of another double bond adds another reactive site for both ionization as well as nucleophilic attack.[5] Such ambiguity can also affect the enantioselectivity significantly with a reasonable expectation for a negative result.

Prior investigations into polylenyl esters for allylic alkylations with palladium generally resulted in linear products.[6] Other metal complexes, including molybdenum and iridium, were found to give the desired branched products in good regio- and enantioselectivities.[7] Recently, Hou and coworkers were the first to report an example of asymmetric allylic alkylation and amination of polyenyl esters using a chiral 1,1′-*P*,*N*-ferrocene palladium complex.[8] However, polyenyl systems bearing an ester in Morita−Baylis−Hillman adducts have not been previously reported.

(1) Tros, B. M., Fleming, I., Eds. *Comprehensive Organic Synthesis*; Pergammon Press: Oxford, England, 1991; Vol. 4, Chapter 3.3.

(2) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759 and references therein.

(3) (a). Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 815−816. (b) Trost, B. M.; Tsui, H. C.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 3534.

(4) For catalytic processes: (a) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219. (b) Iwama, T.; Tsukiyama, S.; Kinoshita, H.; Kanematsu, K.; Tsurukami, Y.; Iwamura, T.; Watanabe, S.; Katoka, T. *Chem. Pharm. Bull.* **1999**, *47*, 956. (c) Barrett, A. G. M.; Cook, A. S.; Kamimura, A. *Chem. Commun.* **1998**, 2533. (d) Hayase, T.; Shibata, T.; Soai, K.; Wakalsuki, Y. *Chem. Commun.* **1998**, 1271. (e) Marko, I. E.; Giles, P. R.; Hindley, N. J. *Tetrahedron* **1997**, *53*, 1015.

(5) For studies on palladium allylic alkylation of dienes, see: Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1998**, *120*, 70.

(6) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1998**, *120*, 70.

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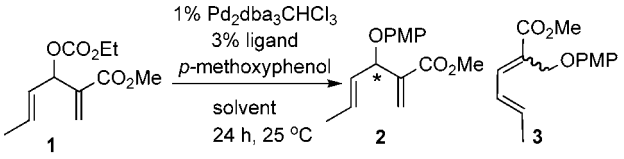
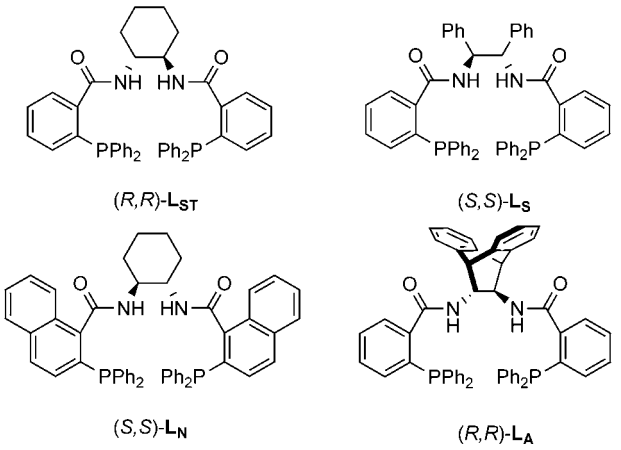
The Morita−Baylis−Hillman adduct from acrylate and crotonaldehyde was employed as the test substrate. Optimization studies of the palladium AAA reaction with *p*-methoxyphenol as the nucleophile with diene **1** as the electrophile are shown in Table 1. Using 3% of the standard

Table 1. Optimization Studies



ligand	solvent[c]	[1]	conversion(%)	ratio[a] (2:3)	ee(%)
(*R*,*R*)-L_{ST}	DCM	0.1 M	100	1:1.2	ND
(*R*,*R*)-L_{ST}	Dioxane	0.1 M	100	2.4:1	ND
(*R*,*R*)-L_{ST}	DMSO	0.1 M	0	----	----
(*R*,*R*)-L_{ST}	DMM	0.1 M	100	1.3:1	ND
(*R*,*R*)-L_{ST}	DME	0.1 M	100	2.8:1	-72
(*R*,*R*)-L_A	DME	0.1 M	100	1.1:1	-72
(*S*,*S*)-L_S	DME	0.1 M	66	15:1	84
(*S*,*S*)-L_N	DME	0.1 M	100	11:1	66
(*S*,*S*)-L_N	DME	0.1 M	100	>20:1[b]	89
(*S*,*S*)-L_N	DME	0.4 M	100	5:1[b]	64



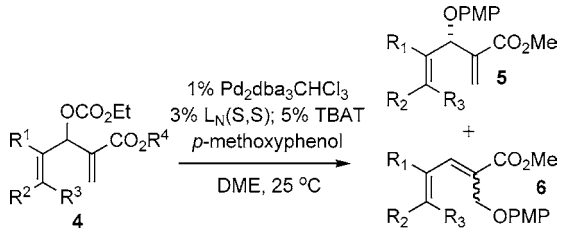
[a] Regioselectivity was determined using ^{1}H NMR ratios. [b] 5% TBAT (tetrabutylammonium triphenyldifluorosilicate) was added to the reaction mixture. [c] DME ≡ 1,2-dimethoxyethane, DCM ≡ dichloromethane, DMM ≡ dimethoxymethane, DMSO ≡ dimethyl sulfoxide. PMP = *p*-methoxyphenol.

Trost ligand (L_{ST}) and 1% Pd_2dba_3·$CHCl_3$ in CH_2Cl_2 as solvent resulted in poor regioselectivity in favor of the undesired isomer (**3**). Switching the solvent to dioxane led to the desired isomer (**2**) as the major product, to the extent of 2.4:1. 1,2-Dimethoxyethane proved to be slightly better than dioxane, with a regioselectivity of 2.8:1, and thus became the solvent of choice for the rest of the optimization studies. Changing ligands had a very pronounced effect, with the Trost anthracenyl ligand (L_A) leading to almost no regioselectivity and the stilbene ligand (L_S) providing the very good regioselectivity (15:1) and enantioselectivity (84%ee). However, the conversion was moderate (66%). Switching to the Trost naphthyl ligand (L_N) increased the conversion satisfactorily but with some loss in regio- and enantioselectivity. On the other hand, addition of 5% TBAT to this catalyst system imparted excellent regioselectivity (>20:1) and enantioselectivity (89%ee). It is known that fluoride and chloride additives attack the palladium of the π allyl complex resulting in greater $\pi-\sigma-\pi$ equilibration.[9] Presumably, speeding up the rate of interconverting unsymmetrical complexes is responsible for this effect as has been the case in previous studies. This conclusion is supported by the effect of concentration. Speeding up the rate of nucleophilic attack by operating at higher concentration decreases selectivity (Table 1, last entry).

With the optimized conditions in hand, several Morita−Baylis−Hillman substrates were prepared and tested in the palladium AAA reaction. Substrates were prepared using the general Morita−Baylis−Hillman conditions with DABCO or with modified versions using methyl propiolate and DIBALH/HMPA or DIBALH/NMO.[10]

Dienes with different substitution patterns as well as different substituents were examined to see what would be tolerated under the reaction conditions (Table 2). When R_1

Table 2. Substrate Scope

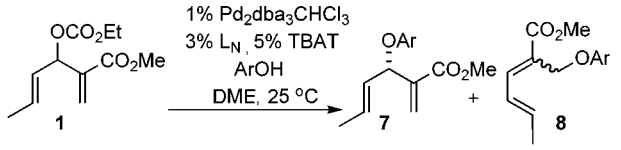


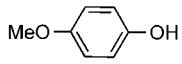
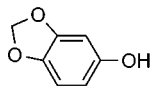
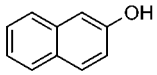
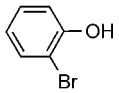
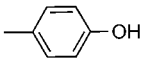
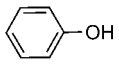
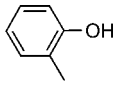
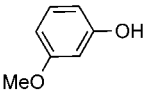
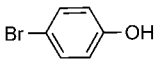
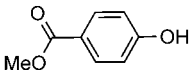
	substituent				conv	ratio	yield	ee
entry	R^1	R^2	R^3	R^4	(%)	(**5**:**6**)	(%)	(%)
1	H	Me	H	OMe	100	>20:1	78	88
2	H	Ph	H	OMe	100	10:1	64	90
3	H	*n*Pr	H	OMe	100	>20:1	66	88
4	H	*i*Pr	H	OMe	100	>20:1	83	89
5	H	Me	Me	OMe	100	>20:1	61	74
6	$(CH_2CH_2)_2$		H	OMe	62	>20:1	56	89
7	Me	Me	H	OMe	75	20:1	58	85
8	H	H	H	OMe	0			
9	Me	H	H	OMe	0			
10	H	2-ClC_6H_4	H	OMe	60	>20:1	61[a]	91
11	H	C_6H_5	H	CH_3	75	7:1	66	86

[a] 100% based on recovered starting material.

and R_3 were hydrogens, the best regio- and enantioselectivities were obtained. The substituent R_2 can be aryl, a straight chain, or a branched alkyl group (entries 1−4). When R_1 and R_2 were alkyl acyclic (entry 5) or alkyl cyclic (entry

Table 3. Oxygen Nucleophiles



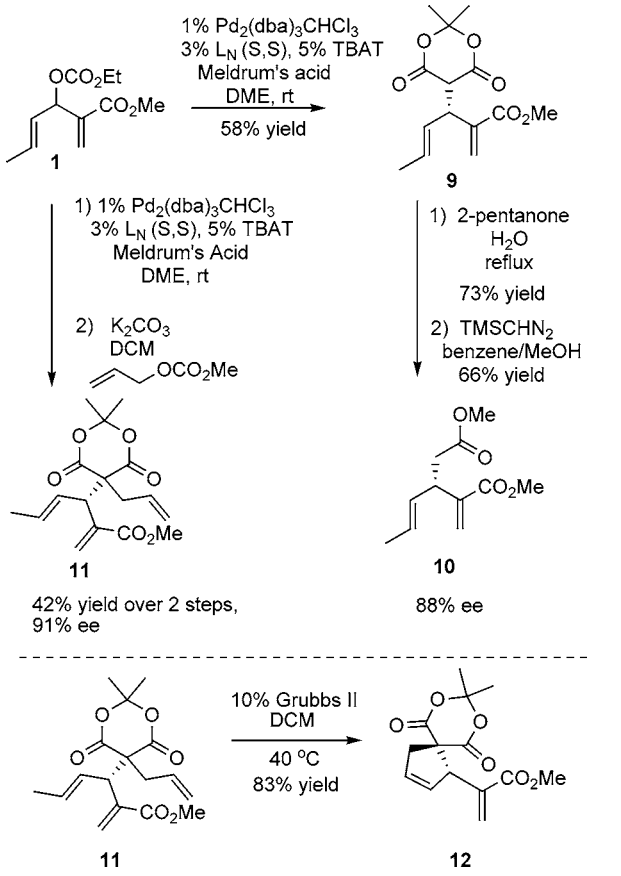
entry	nucleophile	conversion(%)	ratio (7:8)	yield(%)	ee(%)
1		100	>20:1	78	88
2		100	>20:1	61	88
3		0	--	--	--
4		50	0:1	--	--
5		100	>20:1	64	88
6		100	>20:1	68	90
7		50	0:1	--	--
8		100	>20:1	58	92
9		100	13:1	76	78
10		100	6:1	63	65

6), conversion dropped and a slight kinetic resolution resulted as evidenced by the enhanced enantioselectivity of the recovered starting material. As a result, trying to push the reaction to completion in such cases resulted in a drop in enantioselectivity of the desired product as well as a decrease in the regioselectivity.[11] When R_2 and R_3 were hydrogens there was no reaction, even with more reactive phosphate and 2,2,2-trichloroethoxycarbonyl leaving groups. When R_2 was an aromatic ring with a chloride in the meta position, the conversion was only 60%; however, the product was obtained in excellent regio- and enantioselectivity. When the electron-withdrawing ester functionality was replaced with a methyl ketone the regioselectivity eroded but the enantioselectivity remained high (entry 11).

In addition to *p*-methoxyphenol, other phenol nucleophiles were explored using the optimized reaction conditions. Ortho substituents on the phenol were not tolerated, leading to no reaction or formation of the wrong regioisomer (Table 3). When electron-donating substituents were placed on the phenol, the regioselectivity and enantioselectivity were high. Electron-withdrawing groups such as bromide (entry 9) or ester (entry 10) led to diminished regio- and enantioselectivities.

Carbon nucleophiles were also investigated. The typical nucleophiles, such as malonates, malononitrile, and nitromethane, led to either no reaction (in the absence of base) or gave the undesired regioisomer (with added base). However, when Meldrum's acid was used excellent regioselectivity was obtained. The acidity of the C−H proton of Meldrum's acid allows for the standard reaction conditions (without added base), thereby preventing the side reaction of addition to the α,β- unsaturated olefin. The product of

Scheme 1. Carbon Nucleophile



(7) (a) Trost, B. M.; Hildbrand, S.; Dogra, K. *J. Am. Chem. Soc.* **1999**, *121*, 10416. (b) Takeuchi, R.; Tanabe, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 1975. (c) Lipowsky, G.; Helmchen, G. *Chem. Commun.* **2004**, 116. (d) Lipowski, G.; Miller, N.; Helmchen, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 4595.

(8) Zheng, W.-H.; Sun, N.; Hou, X.-L. *Org. Lett.* **2005**, *7*, 5151.

(9) (a). Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545. (b). Burckhardt, U.; Baumann, M.; Togni, A. *Tetrahedron: Asymmetry* **1997**, *8*, 155.

(10) For the method of DIBALH/HMPA, see: Tsuda, T.; Yoshida, T.; Saegusa, T. *J. Org. Chem.* **1988**, *53*, 1037−1040. For the modification with DIBALH/NMO, see: Ramachandran, P. V.; Rudd, M. T.; Burghardt, T. E.; Ram Reddy, M. V. *J. Org. Chem.* **2003**, *68*, 9310.

(11) This was also the only case where the other third possible regioisomer, result from the attack at the carbon bearing R_2 and R_3, was observed. This minor product was formed in slightly higher amounts when the reaction was forced toward completion.

the reaction can be easily hydrolyzed with 2-pentanone/H_2O and then esterified with trimethylsilyldiazomethane. The resulting ester product **10** was isolated in 54% yield and determined by chiral HPLC to have 88% ee from the original palladium-catalyzed AAA reaction (Scheme 1). Also, two sequential palladium alkylation reactions could be done in a one-pot process with Meldrum's acid as a nucleophile. As shown in Scheme 1, compound **1** was the electrophilic partner in the first palladium AAA, and then allyl methylcarbonate was subsequently added to the same reaction to act as the electrophile for the second alkylation reaction. The bisalkylated Meldrum's acid derivative **11** was prepared in 42% yield over two steps and in 91% ee. The use of monomethylated Meldrum's acid as a nucleophile resulted in poorer regioselectivity, presumably due to the increased steric hindrance. The product of bisalkylation, **11**, was then subjected to alkene metathesis using the second-generation Grubbs catalyst in dichloromethane as solvent. Surprisingly, the product from alkene metathesis with the 1,2-disubstituted alkene, rather than with the acrylate, was formed in 83% yield.

The absolute stereochemistry of the product from the addition of *p*-methoxyphenol was determined by deprotection of the aromatic ring with CAN and reaction of the resulting alcohol to form the O-Me mandelate ester.[12] ^{1}H NMR analysis of the diastereomers determined that the (*S*,*S*) enantiomer of the L_N ligand led to the *S* enantiomer of the product as depicted in Figure 1.[13]

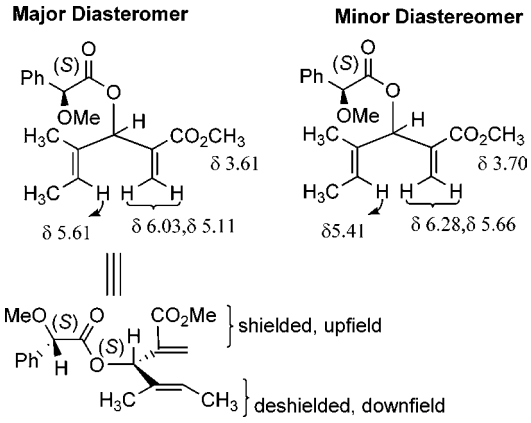
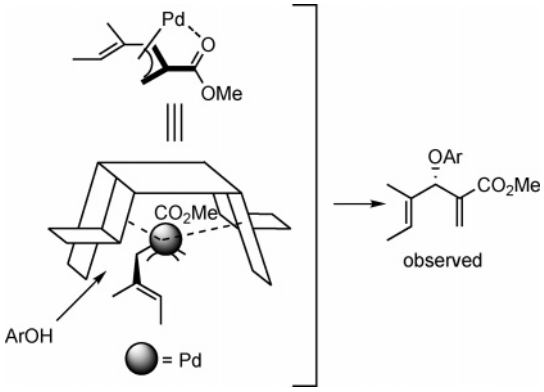


Figure 1. Absolute stereochemistry determination.

This result is consistent with the stereochemistry observed for the simple Morita−Baylis−Hillman adducts and is rationalized using the model for the Trost ligands while invoking palladium coordination of the methyl ester (Scheme 2).[14] Normally, the π-allylpalladium complex adopts the syn conformation to avoid unfavorable steric interactions between substituents of the allyl group with the palladium. However, by placing a methyl ester in the 2 position of the π-allylpalladium complex, interactions of the side chain with the methyl ester become more important, causing the palladium to preferentially adopt the anti-π-allyl geometry. Coordination of the palladium to the methyl ester is also invoked, which changes the cant of the palladium. The nucleophiles prefer to enter under a flap, rather than a wall, thus leading to the observed stereochemistry. The absolute sterochemistry of the adducts with carbon nucleophiles is assigned by analogy.

Scheme 2. Model for Enantioselectivity



In conclusion, Morita−Baylis−Hillman diene adducts have been successfully employed in a palladium-catalyzed asymmetric allylic alkylation reaction with a variety of phenols in good regio- and enantioselectivity. These high enantioselectivities are even more substantial considering the ambiguity introduced by the additional double bond in the allylic system. Meldrum's acid also serves as a nucleophile, providing products that can undergo further manipulations, as well as act as an intermediate in a one-pot tandem palladium AAA reaction. The versatility of these products for a variety of synthetic manipulations was further illustrated by the alkene metathesis to form the asymmetric cyclopentene **12**.

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Supporting Information Available: Full experimental and NMR data for all substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) See the Supporting Information for ^{1}H NMR data.

(14) Trost, B. M.; Machacek, M. R.; Tsui, H. C. *J. Am. Chem. Soc.* **2005**, *127*, 7014.