

Catalytic Enantioselective Diels-Alder Reactions of Acrylate Derivatives in the Presence of Chiral Binap-Palladium Complexes

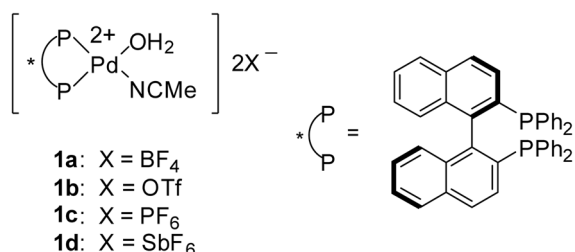
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The Diels-Alder reaction is one of the most efficient C-C bond-forming reactions that permit the rapid development of molecular complexity.¹ It allows the stereoselective formation of as many as four stereogenic centers, and as many as three carbocyclic rings in the intramolecular and transannular variations. For this reason, the recent development of highly enantioselective Diels-Alder reactions represents a great advance in synthetic chemistry.¹ Remarkable progress toward this goal has been achieved through the use of both chiral auxiliaries² and chiral catalysts such as metal complexes³ and organocatalysts.⁴ A large number of Lewis acid catalysts based on aluminum, boron, magnesium, and transition metals have been used for this purpose.³ Recently, the potential of late transition metal such as palladium-based chiral Lewis acids has been explored in detail for Diels-Alder reactions.⁵ While several efficient asymmetric Diels-Alder reactions using chiral Lewis acids have been developed, a drawback is that most Lewis acids are unstable in the presence of water and even sensitive to moisture. Therefore, the development of Diels-Alder reaction using moisture-stable chiral Lewis acid is still in great demand.

As part of research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,⁶ we report the catalytic enantioselective fluorination and amination of ester derivatives promoted by air- and moisture-stable chiral palladium complexes.⁷ In this letter, we wish to report the Diels-Alder reactions of acrylate attached to a two-point donor in the presence of chiral palladium complexes **1**.⁸



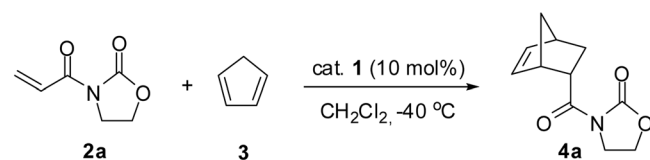
To determine suitable reaction conditions for the catalytic enantioselective Diels-Alder reactions of acrylates, we initially investigated the reaction system with cyclopentadiene **3** and acrylate derivatives **2** capable of forming six- or five-membered chelate with the chiral (*R*)-Binap-palladium complexes **1c** in dichloromethane. The oxazolidinone template **2a** showed excellent diastereoselectivity (*endo/exo* 98/2) and

enantioselectivity, 99% ee (entry 1). Replacement of the ring oxygen in **2a** by a methylene group, the pyrrolidinone template **2b**, gave slightly lower reactivity and selectivity (entry 2). The *N*-benzoyl and *N*-2-pyridyl templates **2c-2d** were less reactive and less selective as compared to template **2a** (entries 3 and 4). Peplacement of benzoyl group in **2c**, with phosphoryl group as in **2e**, led to lowered reactivity. Two

Table 1. Enantioselective Diels-Alder reaction of acrylate templates

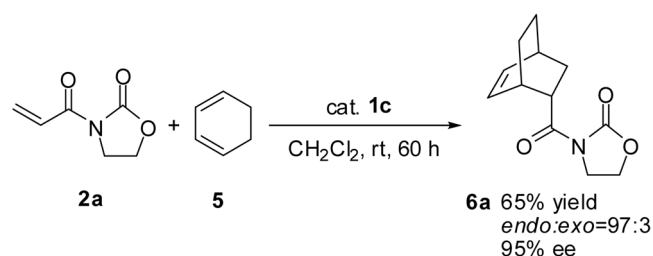
Entry	2 , Z	Temp (°C), time (h)	Yield (%)	<i>endo/exo</i>	<i>endo</i> ee ^a (%, config) ^b
1		rt, 1.5	93	93 / 7	57 (<i>S</i>)
	2a	-40, 5	97	98 / 2	99 (<i>S</i>)
2		rt, 7	97	87 / 13	77 (<i>S</i>)
	2b	-40, 7	97	89 / 11	85 (<i>S</i>)
3		rt, 0.3	99	90 / 10	77
	2c	-40, 8	99	96 / 4	90
4		rt, 2	89	79 / 21	60
	2d	-40, 150	53	79 / 21	85
5 ^c		rt, 22	43	59/41	27
	2e				
6		rt, 9	92	92 / 8	5
	2f	-40, 264	72	94 / 6	11
7 ^d		rt, 0.7	74	90 / 10	37
	2g	-40, 13	72	93 / 7	57

^aEnantiopurity of **4** was determined by HPLC analysis with Chiralcel OD-H (for **4a**, **4f**), OJ (for **4c**), Chiralpak AD (for **4b**), and AD-H (for **4d**, **4e**, **4g**) column. ^bAbsolute configuration was determined by comparison of the optical rotation and the HPLC retention time of the corresponding adduct with literature value.^{3d} ^cDephosphorylation product was obtained as major product. ^dDesilylation product was obtained as major product.

Table 2. Enantioselective Diels-Alder reaction of cyclopentadiene **3** with dienophile **2a** in presence of Pd complexes


Entry	Cat.	Time (h)	Yield (%)	Endo/exo	Ee (%) ^{a,b}
1	1a	32	71	95 / 5	99 (S)
2	1b	45	32	96 / 4	87 (S)
3	1c	5	97	98 / 2	99 (S)
4	1d	45	40	97 / 3	90 (S)
5 ^c	1c	19	89	95 / 5	99 (S)

^aEnantiopurity of **4a** was determined by HPLC analysis with Chiralcel OD-H column. ^bAbsolute configuration was determined by comparison of the optical rotation and the HPLC retention time of the corresponding ester with literature value.^{3d} ^cReaction carried out using 5 mol% of catalyst.

**Scheme 1**

templates **2f** and **2g** capable of five-membered chelate with the palladium complex were examined. Both of these templates showed only moderate selectivity (entries 6 and 7) as compared to reactions with acrylates derived **2a-2d**.

Catalysts **1a** and **1c** were more effective than other catalysts (Table 2, entries 1-4). The present catalytic system tolerates catalyst loading down to 5 mol % without compromising either the yield or enantioselectivity (entries 3 and 5).

Another diene, 1,3-cyclohexadiene (**5**) was also examined in this reaction with 3-acryloyl-2-oxazolidinone (**2a**) and the result showed excellent diastereoselectivity, 97/3 *endo*/*exo* ratio in 65% yield, the *endo* isomer showed high enantioselectivity, 95% ee (Scheme 1). Unfortunately, the reaction of β -alkyl substituted acryloyl derivatives with cyclopentadiene was not preceded in this condition.

In conclusion, we have developed a highly efficient catalytic enantioselective Diels-Alder reaction of acrylates using air- and moisture-stable chiral palladium complexes. The desired Diels-Alder adducts were obtained in good to high yields, and excellent enantioselectivities (up to 99% ee) were observed. Further details and application of this Diels-Alder reaction will be presented in due course.

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- Typical procedure for the Diels-Alder reaction of acrylate derivatives in the presence of chiral Binap-palladium complexes:** To a solution of Pd-cat. **1c** (0.01 mmol, 10.8 mg) in CH₂Cl₂ (1 mL) was added acryloyl-1,3-oxazolidinone-2-one (**2a**, 0.1 mmol, 14.1 mg). After the mixture was cooled to -40 °C, cyclopentadiene (**3**, 0.5 mmol, 0.04 mL) was added. The reaction mixture was stirred at -40 °C for 5 h. The reaction mixture was quenching with saturated NH₄Cl and extracted with dichloromethane. The combined organic layers were dried over MgSO₄, filter, concentrated, and purified by flash chromatography (ethyl acetate, hexane 1:1) to afford the cycloadduct **4a** (20.1 mg, 97%).