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Decarbonylative Cycloaddition of Phthalic Anhydrides with Allenes

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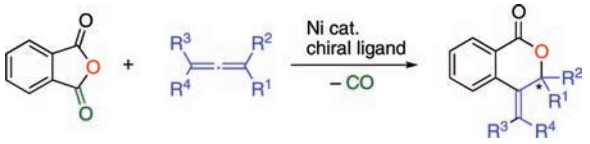
ABSTRACT



The decarbonylative cycloadditions of phthalic anhydrides with allenes were performed by using nickel catalyst. The asymmetric variant of the cycloaddition was also achieved by using chiral phosphine ligands to provide δ-lactones enantioselectively.

Transition-metal-catalyzed insertion reactions of an unsaturated carbon–carbon bond into a carbon–oxygen bond should be one of the most useful transformations, since the reaction forms carbon–carbon and carbon–oxygen bonds simultaneously.[1,2] Herein, we report our results of a regioselective decarbonylative cycloaddition of phthalic anhydrides with allenes to provide δ-lactones (Scheme 1). The reaction represents an unprecedented insertion reaction of a carbon–carbon double bond into a carbon–oxygen bond. The strategy is also applicable for cycloaddition of thiophthalic anhydrides with allenes to give δ-thiolactones, which also represents the first example of a nickel-catalyzed insertion reaction of a carbon–carbon double bond into a carbon–sulfide bond.[3–8] Asymmetric variants of both the cycloadditions were also examined by using chiral phosphine ligands.[9,10]

We first examined the ligand effects in the decarbonylative cycloaddition of phthalic anhydride (**1**) with allene **2a** using Ni(cod)$_2$ as a Ni(0) precursor. The reaction was performed in refluxing acetonitrile (MeCN) for 12 h,[11]

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[11] The reaction did not proceed in a sealed vessel. Refluxing of reaction solvent is probably essential to promote the exhaust of CO from the reaction system efficiently.

10.1021/ol200044y

Scheme 1. Nickel-Catalyzed Decarbonylative Cycloaddition of a Phthalic Anhydride with an Allene

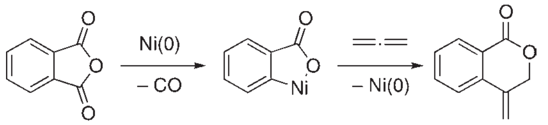
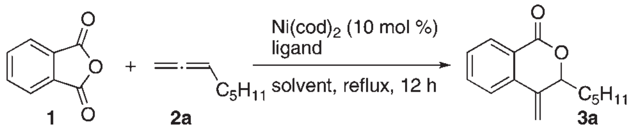


Table 1. Optimization of Reaction Conditions for the Nickel-Catalyzed Decarbonylative Cycloaddition of a Phthalic Anhydride **1** with an Allene **2a**[a]



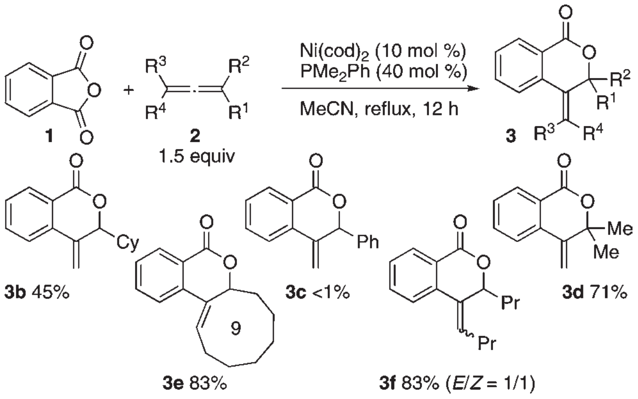
entry	ligand (mol %)	**2a** (equiv)	solvent	yield (%)[b]
1	PMe_3 (40)	1	MeCN	43
2	PMe_2Ph (40)	1	MeCN	52
3	$PMePh_2$ (40)	1	MeCN	46
4	PPh_3 (40)	1	MeCN	<1
5	PCy_3 (20)	1	MeCN	<1
6	bpy (20)	1	MeCN	<1
7	PMe_2Ph (40)	1.5	MeCN	64
8	PMe_2Ph (40)	3	MeCN	52
9	PMe_2Ph (40)	1	MeCN	52
10	PMe_2Ph (40)	1.5	dioxane	61
11	PMe_2Ph (40)	1.5	pyridine	59
12	PMe_2Ph (40)	1.5	toluene	53

[a] Reactions were carried out using Ni(cod)$_2$ (10 mol %), ligand, **1** (0.5 mmol), and **2** in 1 mL of refluxing solvent for 12 h. [b] Isolated yields.

and the results are summarized in Table 1. Among the ligands examined, PMe_2Ph gave the best result to afford δ-lactone **3a** in 52% yield regioselectively (entry 2). Trace or lower amounts of **3a** were obtained in the cases of using PPh_3, PCy_3, and bpy in place of PMe_2Ph (entries 4−9). It was found that the reaction of **1** with 1.5 equiv of **2a** gave the highest yield of **3a** in 64% yield (entry 7). In other solvents such as 1,4-dioxane, pyridine, and toluene, yields were even lower (entries 10−12). On addition of $ZnCl_2$ (20 mol %), the cycloaddition was retarded.[1]

We next investigated the scope of the reaction using various allenes, and the results are summarized in Scheme 2. The reaction of cyclohexyl-substituted allene **2b** with **1** afforded **3b** in 45% yield, while phenyl-substituted allene **2c** failed to participate in the reaction and recovered unchanged. This feature may suggest that an electron-rich double bond contributes significantly toward the reactivity on the cycloaddition. Indeed, the reaction of *gem*-dimethyl-substituted allene **2d** reacted with **1** to provide a single product **3d** via regioselective insertion of the internal carbon−carbon double bond of **2d**. The cycloaddition of a cyclic allene **2e** gave **3e** in excellent yield, while the reaction of 1,3-dipropyl-substituted allene **2f** gave cycloadduct **3f** as a 1/1 mixture of regioisomers in 83% yield.

Scheme 2. Scope of the Nickel-Catalyzed Decarbonylative Cycloadditions of Phthalic Anhydride **1** with Allenes **2**



These results prompted us to investigate an asymmetric decarbonylative cycloaddition of phthalic anhydride **1** with alkene **2a** by using a chiral ligand in place of PMe_2Ph (Table 2). The reactions with chiral bidentate phosphine ligands, such as (*S*,*S*)-chiraphos[12] or (*R*,*R*)-Me-duphos,[13] gave small amounts of cycloadduct **3a** but without enantioselectivity (entries 1−2). Optically active **3a** was obtained in 55% yield when (*R*)-binap was used as a ligand.[14] The reaction with (*R*)-quinap did not afford any cycloadduct at all,[15] while bidentate P−N ligands, such as (*S*)-*i*Pr-fox[16] or (*S,S*)-*i*Pr-foxap,[17] gave improved results in terms of both yield and selectivity (entries 5 and 8). The yield and the enantioselectivity were influenced by the reaction medium employed. The highest yield and enantioselectivity were observed when pyridine was used as the reaction solvent, and **3a** was obtained in 73% yield with 59% *ee* (entry12). With a shorter reaction time (4 h), **3a** was obtained in 56% yield with 58% *ee*. Phthalic anhydride **1** also reacted with **2b** to provide **3b** in 64% yield with 81% *ee* (entry 14).

In addition to phthalic anhydride, thiophthalic anhydride **4** also participated in the reaction with allenes **2** (Scheme 3). Cycloaddition of thiophthalic anhydride **4** with 1.5 equiv of allene **2a** in the presence of Ni/PMe_2Ph catalysis provided δ-thiolactone **5a** in 93% isolated yield. The use of a different ligand, such as PMe_3, PPh_3, or PCy_3, in toluene gave inferior results. The reaction of cyclohexyl-substituted allene **2b** with **4** gave the correspondingly substituted cycloadduct **5b** in 87% yield with a regioselectivity of 10/1. Phenyl-substituted allene **2c** also participated in the reaction to give **5c** in 87% yield with a 5/1 ratio of regisoisomers. *gem*-Dimethyl-substituted allene **2d** reacted

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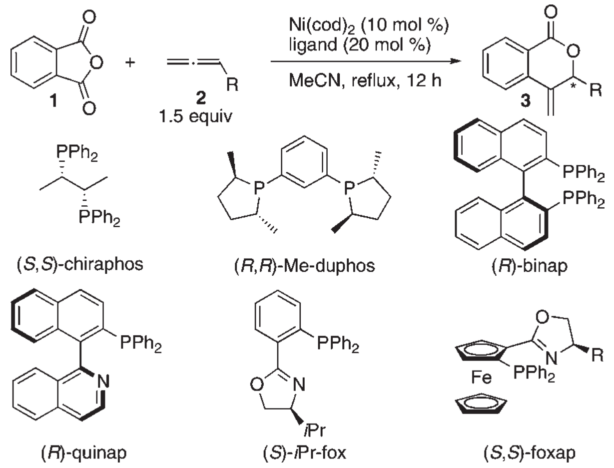
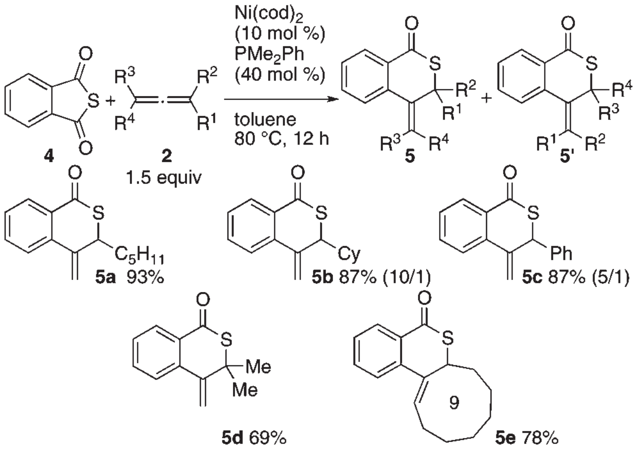
Table 2. Nickel-Catalyzed Asymmetric Decarbonylative Cycloaddition of Phthalic Anhydrides **1** with Allenes **2**[a]



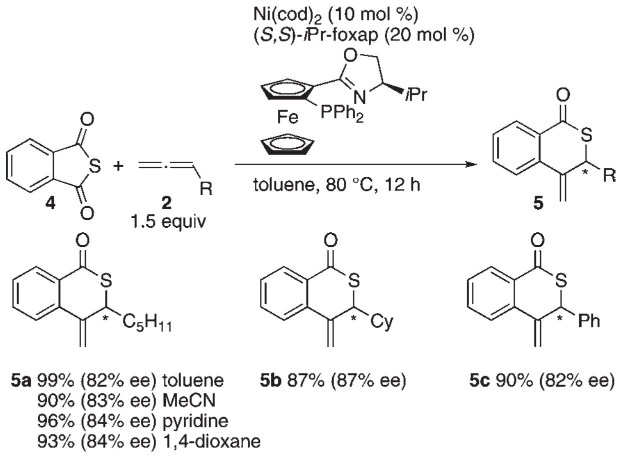
entry	R	chiral ligand	solvent	yield (%)[b]	ee (%)
1	C_5H_{11} (**2a**)	(*S*,*S*)-chiraphos	MeCN	7	<1
2	C_5H_{11} (**2a**)	(*R*,*R*)-Me-duphos	MeCN	5	<1
3	C_5H_{11} (**2a**)	(*R*)-binap	MeCN	55	7
4	C_5H_{11} (**2a**)	(*R*)-quinap	MeCN	<1	–
5	C_5H_{11} (**2a**)	(*S*)-*i*Pr-fox	MeCN	77	30
6	C_5H_{11} (**2a**)	(*S*,*S*)-Bn-foxap	MeCN	67	<1
7	C_5H_{11} (**2a**)	(*S*,*S*)-Ph-foxap	MeCN	70	3
8	C_5H_{11} (**2a**)	(*S*,*S*)-*i*Pr-foxap	MeCN	70	39
9	C_5H_{11} (**2a**)	(*S*,*S*)-*t*Bu-foxap	MeCN	37	20
10	C_5H_{11} (**2a**)	(*S*,*S*)-*i*Pr-foxap	toluene	70	<1
11	C_5H_{11} (**2a**)	(*S*,*S*)-*i*Pr-foxap	1,4-dioxane	48	<1
12	C_5H_{11} (**2a**)	(*S*,*S*)-*i*Pr-foxap	pyridine	73	59
13	C_5H_{11} (**2a**)	(*S*,*S*)-*i*Pr-foxap	pyridine	56[c]	58
14	Cy (**2b**)	(*S*,*S*)-*i*Pr-foxap	pyridine	64	81

[a] Reactions were carried out using Ni(cod)$_2$ (10 mol %), ligand, **1** (0.5 mmol), and **2** in 1 mL of refluxing solvent for 12 h . [b] Isolated yields. [c] Reaction time: 4 h.

Scheme 3. Scope of the Nickel-Catalyzed Decarbonylative Cycloaddition of Thiophthalic Anhydride **4** with Allenes **2**



Scheme 4. Nickel-Catalyzed Asymmetric Decarbonylative Cycloaddition of Thiophthalic Anhydride **4** with Allene **2**



with **4** to furnish a single product **5d**. The reaction was also compatible with a cyclic allene **2e** to give **5e** in 78% yield.

The cycloaddition was also extended to asymmetric reactions. The reaction of **4** with **2a** affords **5a** in 99% yield with 82% *ee* when (*S*,*S*)-*i*Pr-foxap was employed as a chiral phosphine ligand (Scheme 4). Only minor solvent effects on enantioselectivity and yield were observed. Under the same reaction conditions, monosubstituted allene such as **2b** and **2c** reacted with **4** to afford the correspondingly substituted optically active cycloadducts **5b** and **5c** in excellent yields.

Furthermore, the enantio- and regioselective cycloaddition of phthalimide with allene was briefly examined (Scheme 5).[18,19] The reaction of *N*-pyrrol-substituted phthalimide **6** with allene **2a** for 12 h afforded cycloadduct **7a** in 48% yield with 82% *ee*. Monosubstituted allene **2b** also reacted with **6** to afford the correspondingly substituted optically active cycloadducts **7b** and in 40% yield (82% *ee*), while phenyl-substituted allene **2c** did not participate in the reaction.

A plausible reaction pathway to account for the formation of cycloadducts **3**, **5**, and **7** based on the observed results is outlined in Scheme 6. The catalytic cycle of the

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(18) (a) Kajita, Y.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2008**, *130*, 6058. (b) Fujiwara, K.; Kurahashi, T.; Matsubara, S. *Org. Lett.* **2010**, *12*, 4548.

(19) For oxidative addition of C–N bond to Ni, see: (a) Chan, Y. W.; Renner, M. W.; Balch, A. L. *Organometallics* **1983**, *2*, 1888. (b) Lin, B. L.; Clough, C. R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 2890. (c) Ozerov, O. V.; Guo, C.; Fan, L.; Foxman, B. M. *Organometallics* **2004**, *23*, 5573.

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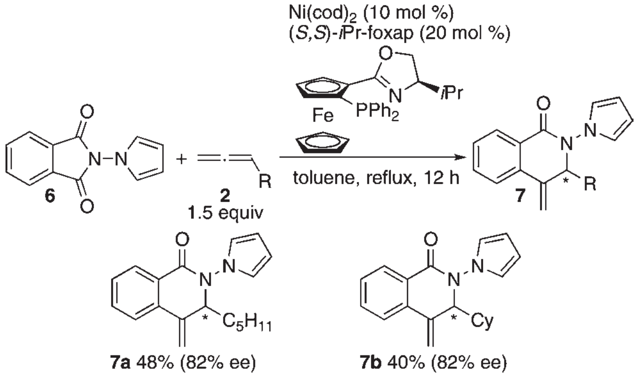
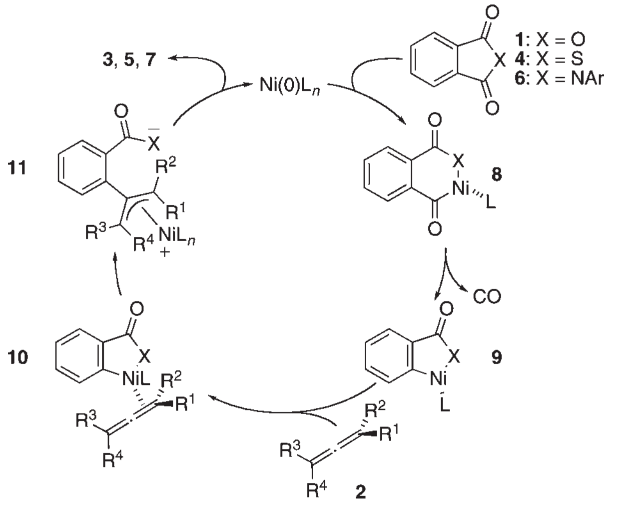
Scheme 5. Nickel-Catalyzed Asymmetric Decarbonylative Cycloaddition of Phthalimide **6** with Allenes **2**



Scheme 6. Plausible Reaction Pathway for the Nickel-Catalyzed Decarbonylative Cycloadditions



present reactions may consist of oxidative addition of a CO−X bond to a Ni(0) complex.[1,5,19−22] Subsequent decarbonylation and coordination of allene **2** take place to give nickel(II) intermediate **10**. The allene would then insert into the C−Ni bond to give the more stable acyclic π-allylnickel intermediate **11**.[23,24] Nucleophilic addition of a heteroatom onto π-allylnickel at the more substituted carbon takes place to afford cycloadducts and regenerate the starting Ni(0) complex.

In summary, we have developed a decarbonylative cycloaddition of phthalic anhydride with allene to give δ-lactone in a single step. The reaction represents an unprecedented insertion reaction of a carbon−carbon double bond into a carbon−oxygen bond. We also demonstrated for the first time that δ-thiolactone can be prepared via decarbonylative cycloaddition of thiophthalic anhydride with allene.[25] Moreover, asymmetric insertion reactions of a carbon−carbon double bond into a carbon−oxygen bond and into a carbon−sulfide bond were also successfully demonstrated with chiral phosphine ligands to provide δ-lactones and δ-thiolactones.

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

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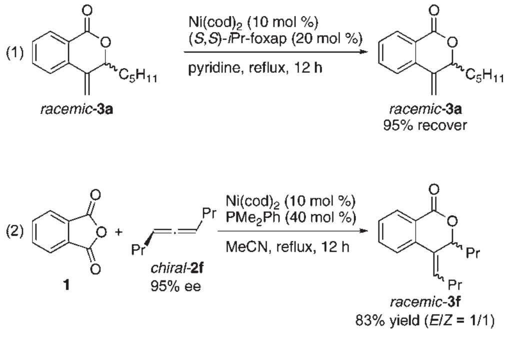
(23) For migratory insertion of allenes into oxanickelacycles, see: Hoberg, H.; Peres, Y.; Krüger, C.; Tsay, Y.-H. *Angew. Chem., Int. Ed.* **1987**, *26*, 771.

(24) It was found that racemic cycloadduct **3a** was recovered unchanged when it was subjected to the Ni/(*S*,*S*)-*i*Pr-foxap catalyst (1). This result may indicate that a reductive elimination step is an irreversible process. Meanwhile, the reaction of phthalic anhydride **1** with chiral allene **2f** (95% *ee*) in the presence of the Ni/PMe$_2$Ph catalyst gave racemic cycloadducts **3f** (2). This may clearly suggest that the reaction proceeds via π-allylnickel **11**, which is a key intermediate for chiral induction.



(25) Functionalized δ-lactones are ubiquitous in a variety of biologically active natural products. For recent examples, see: (a) Munro, T. A.; Rizzacasa, M. A.; Roth, B. L.; Toth, B. A.; Yan, F. *J. Med. Chem.* **2005**, *48*, 345. (b) Nicotra, V. E.; Gil, R. R.; Oberti, J. C.; Burton, G. *J. Nat. Prod.* **2007**, *70*, 808. (c) Thompson, C. M.; Quinn, C. A.; Hergenrothe, P. J. *J. Med. Chem.* **2009**, *52*, 117. (d) Meragelman, T. L.; Scudiero, D. A.; Davis, R. E.; Staudt, L. M.; McCloud, T. G.; Cardellina, J. H., II; Shoemaker, R. H. *J. Nat. Prod.* **2009**, *72*, 336. (e) Haritakun, R.; Sappan, M.; Suvannakad, R.; Tasanathai, K.; Isaka, M. *J. Nat. Prod.* **2010**, *73*, 75.