

Highly Diastereo- and Enantioselective Pd-Catalyzed Cyclopropanation of Acyclic Amides with Substituted Allyl Carbonates

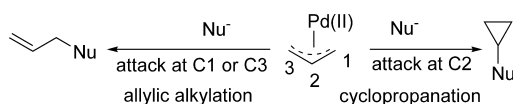
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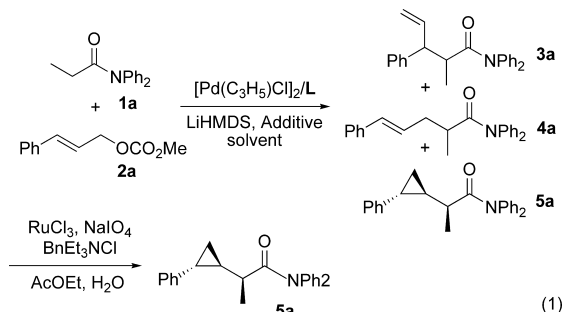
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As one of the most investigated reactions in transition metal catalysis, palladium-catalyzed asymmetric allylic alkylation reaction has showed its great power in the enantioselective formation of C–C bonds.¹ In most cases, the products were formed via attack of nucleophiles to the terminal carbon of π -allyl-Pd intermediates. Hegedus was the first to demonstrate the formation of cyclopropane by the reaction of π -allylpalladium chloride with ester enolates via attack of nucleophiles to the central carbon in 1980 (Scheme 1).^{2,4g} Since, some procedures have been developed for the formation of cyclopropanes via Pd-mediated reaction of a carbon nucleophile.^{3,4} However, few examples have been realized for the cyclopropanation reaction by using catalytic amounts of Pd-complexes to date,⁴ and only one report succeeded in an asymmetric catalytic version with moderate ee by Satake.⁵ Pd-catalyzed asymmetric cyclopropanation reaction with an allyl reagent is still a far less explored field. Recently, we have showed the use of a “hard” carbanion in Pd-catalyzed asymmetric allylic alkylation successfully.^{6,7} Here, we disclose our preliminary results on the Pd-catalyzed cyclopropanation of acyclic amides with monosubstituted allyl carbonates with high diastereo- and enantioselectivities using our SiocPhox ligand.⁸

Scheme 1. Pd-Catalyzed Allylic Substitution and Cyclopropanation



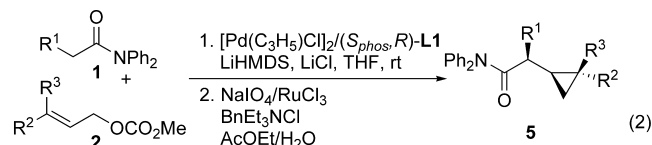
The investigation was initiated from the reaction of amide **1a** with cinnamyl methyl carbonate **2a** by using SiocPhox (*R*_{phos},*R*)-**L1** as the ligand, obtaining branched and linear allylated products **3a** and **4a** in a ratio of 4:1. However, cyclopropanation product **5a** was obtained predominantly if SiocPhox (*S*_{phos},*R*)-**L1** was used (eq 1). Although we failed to separate the products, **3a** and **4a** were removed by oxidation using RuCl₃/NaIO₄ and **5a** was obtained exclusively in 60% yield. The stereochemistry of the major diastereoisomer of **5a** was determined by its 2D-NMR (See Supporting Information (SI)).



To improve the results of this cyclopropanation reaction, the influence of the reaction parameters was studied (Table 1). It was found

that the presence of LiCl had a great impact on the selectivity of cyclopropanation/allylic alkylation (*c/a* selectivity) as well as diastereoselectivity of cyclopropanation.^{7c,d,9} The reaction provided **5a** with a *c/a* selectivity of 65/35 and *dr* ratio of 5:1 in the absence of LiCl, while both *c/a* selectivity and *dr* ratio increased to 80/20 and 12:1, respectively, when 100 mol % of LiCl was added (entry 2 vs 1). Both *c/a* selectivity and *dr* ratio of **5a** were lower if nonchloro additives were used (entries 3–5), which were improved if Bn₄NCl or NaCl was used (entries 8 and 9). The importance of the lithium ion was revealed from the reaction using NaHMDS or KHMDS as the base; in both cases the selectivities were lower (entries 10 and 11). The role of LiCl is confirmed further by the control experiments. The reaction provided low yields of cyclopropane products with low *c/a*-, diastereo- and enantioselectivities using Pd(dba)₂/(*S*_{phos},*R*)-**L1** with no additive, but they increased greatly if 10 mol % of LiCl was added (entry 6 vs 7). The investigation of the effect of solvents on the reaction revealed that THF was the best among the solvents screened (entry 2 vs entries 14–17). Little fluctuations of yield and selectivity of the reaction were found when the reaction proceeded at a temperature between 0 to 40 °C (not shown in table).

The substituent on the oxazoline ring of the ligand has an important influence on the reaction.^{6c,d,8,10} Low yield with low *c/a*- and diastereoselectivities was given when SiocPhox (*S*_{phos},*R*)-**L2** with an *i*-Pr group on the oxazoline ring was used as the ligand (entry 12). An even worse result was provided when (*S*_{phos},*R*)-**L3** with a *t*-Bu group on the oxazoline ring was used (entry 13). Lower reactivity and *c/a*- and diastereoselectivities were also found when allyl acetate or branched allyl carbonate was used (not shown in table; see SI).



Under the optimized reaction conditions different amides and monosubstituted allyl reagents were examined, and the results are compiled in Table 2. In general, the reaction proceeded smoothly to afford the cyclopropane products **5** in good yields after removal of allylation products by oxidation. Three chiral centers were established in high diastereo- and enantioselectivities, the *dr* ratio being 4–30 and the ee value being 83–98%. The acyclic amides with different lengths of chain are suitable substrates to provide the cyclopropanes **5** in high

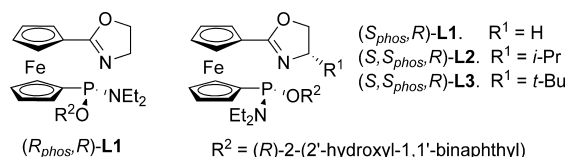
Figure 1. Ferrocene-based ligands SiocPhox **L1**–**L3**.[†] State Key Laboratory of Organometallic Chemistry.[‡] Department of Analytic Chemistry.

Table 1. Effects of Additives and Solvents on the Pd-Catalyzed Reaction of **1a** and **2a**^a

entry	solvent	additive ^b	3a:4a:5a ^c	5a		
				yield% ^d	d.r. ^e	ee% ^f
1	THF	—	6:29:65	60	5:1	93
2	THF	LiCl	6:14:80	73	12:1	95
3	THF	LiBr ^g	11:19:70	58	6:1	84
4	THF	LiClO ₄ ^g	20:33:47	40	3:1	32
5	THF	LiI	8:80:12	—	4:1	—
6	THF	— ^g	8:31:61	47	5:1	84
7	THF	LiCl ^{h,g}	7:19:74	62	9:1	93
8	THF	Bn ₄ NCl	5:26:69	50	11:1	94
9	THF	NaCl	7:25:68	51	8:1	91
10	THF	NaCl ⁱ	23:17:60	46	3:1	89
11	THF	KCl ^j	—	trace	—	—
12 ^k	THF	LiCl	6:77:17	24 ^l	5.4:1	—
13 ^m	THF	LiCl	—	trace	—	—
14	toluene	LiCl	13:28:59	24	3:1	75
15	Et ₂ O	LiCl	14:35:51	25	3:1	72
16	dioxane	LiCl	16:25:59	40	5:1	80
17	DME	LiCl	10:14:76	46	11:1	93

^a Molar ratio of **1a**/[Pd(C₃H₅)Cl]₂/(*S*_{phos}:*R*)-**L1**/LiHMDS/**2a** = 100/2/4/100/120. ^b 100 mol % of additive was used. ^c Determined by GC. ^d Isolated yield of **5a**. ^e D.r. of **5a**, the structure of minor diastereoisomers was not determined. ^f Determined by chiral HPLC. ^g Pd(dba)₂ was used. ^h 10 mol % of LiCl was added. ⁱ NaHMDS as the base. ^j KHMDS as the base. ^k **L2** was used. ^l Isolated yield of **3a**, **4a** and **5a**. ^m **L3** was the ligand.

Table 2. Pd-Catalyzed Cyclopropanation of Acyclic Amides **1** with Allyl Carbonates **2a**

entry	R ¹	R ²	R ³	5		
				yield% ^b	d.r. ^c	ee% ^d
1	Me	Ph	H	a , 73	12:1	95
2	Et	Ph	H	b , 72	12:1	97
3	<i>n</i> Pr	Ph	H	c , 72	4:1	94
4	<i>i</i> Pr	Ph	H	d , 83	6:1	96
5	Me	<i>p</i> -MeC ₆ H ₅	H	e , 69	15:1	94
6	Me	<i>p</i> -MeOC ₆ H ₅	H	f , 68	23:1	96
7	Me	<i>p</i> -FC ₆ H ₅	H	g , 67	11:1	84
8	Me	<i>p</i> -ClC ₆ H ₅	H	h , 68	7:1	91
9	Me	<i>p</i> -BrC ₆ H ₅	H	i , 67	8:1	83
10	<i>i</i> Pr	<i>p</i> -BrC ₆ H ₅	H	j , 74	5:1	92
11	Me	1-Naphthyl	H	k , 68	8:1	93
12	Me	Ph	Me	l , 37	30:1	98
13	Me	Me	H	m , 18	3:1	89

^a Molar ratio of **1**/[Pd(C₃H₅)Cl]₂/(*S*_{phos}:*R*)-**L1**/LiHMDS/**2**/LiCl = 100/2/4/100/120/100. ^b Isolated yield of **5**. ^c D.r. of **5** determined by GC, the structure of minor diastereoisomers was not determined. ^d Determined by chiral HPLC.

ee (entries 1–4 and 10), though the diastereoselectivity decreased when the R¹ group of **1** was *n*-Pr (entry 3) or *i*-Pr (entries 4 and 10). However, the reaction of isobutanamide failed to give the desired product (not shown in table). The electronic property of the substituent on the phenyl ring in allyl reagents **2** has some impact on the diastereo- and enantioselectivities of the reaction. The presence of an electron-donating group in **2** favored the gain of **5** in higher diastereo- and enantioselectivities (entries 5 and 6 vs 7–10). Cyclopropane product **5k** in higher enantioselectivity was also obtained when naphthyl substituted carbonate **2** was used (entry 11). Note that *gem*-disubstituted allyl carbonate could also be used, providing **5l** with a chiral quaternary carbon center on the cyclopropane ring with even higher diastereo- and enantioselectivities, the dr ratio being 30:1 and ee being 98%, albeit the yield was lower (entry 12).¹¹ When crotyl carbonate was the reagent, high enantioselectivity was given, but the yield and diastereoselectivity were

low (entry 13).¹¹ The use of aliphatic allyl reagents in the reaction is still a challenge.

The absolute configuration of **5j** was determined as (*S*,*R*,*R*) via its X-ray diffraction analysis. This result provides support of the NMR assignment of stereochemistry of **5a** mentioned before.

The present report realized the asymmetric cyclopropanation reaction of acyclic amides with monosubstituted allyl substrates in the presence of Pd-catalyst. Cyclopropane derivatives with three chiral centers were provided with high diastereo- and enantioselectivities. The impact of LiCl on the *c/a*- and diastereoselectivities was demonstrated. Further investigations on the role of the ligand and the reaction mechanism in detail as well as on the extension of the reaction scope and applications of this methodology in organic synthesis are in progress.

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Supporting Information Available: General procedure for the Pd-catalyzed cyclopropanation, NMR spectra and HPLC data for **5**, cif file of X-ray diffraction analysis of **5j**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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