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Ni-Catalyzed Asymmetric Reductive Allylation of Aldehydes with Allylic Carbonates

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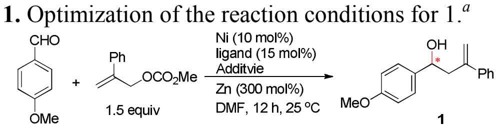
This work features first asymmetric Ni-catalyzed reductive coupling of allylic carbonates with aldehydes, which may proceed via allyl-Ni intermediates although Zn was used as the terminal reductant. Moderate to excellent enantiomeric excess were obtained with excellent functional group tolerance.

Asymmetric carbonyl allylation represents one of the most important reaction types in the current organic synthesis.[1] In particular, the reductive protocols that employ allylic and carbonyl electrophiles without pre-preparation of allylic nucleophiles has received significant advances.[2-9] In addition to the well-established Ni-catalyzed Nozaki-Hiyama-Kishi (NHK) method,[2] In-, Zn-, Et_3B-, and $SnCl_2$-mediated Barbier allylation of aldehydes with allyl halides have also been well studied. However, the catalytic asymmetric Barbier method appears to be difficult, which generally requires stoichiometric amount of chiral auxiliaries.[3] The employment of more accessible and stable allylic alcohols and their derivatives such as allylic acetates and carbonates has drawn increasing attention in realizing highly enantioselective allylation of carbonyl compounds.[4-9] However, the transition metals involved in these reductive umpolung catalytic processes are primarily limited to palladium and iridium.[5-8] For instance, Krische has developed an elegant Ir-catalyzed transfer hydrogenation method allowing alcohols serving as the substrates and reducing reagents, which sets a high bar in the sense of green carbonyl allylation.[6,7] Zanoni and Zhou have demonstrated that catalytic Pd/phosphines in combination with Et_2Zn and Et_3B generate homoallylic alcohols with high enantioselectivities, respectively.[8] Therefore, the development of asymmetric reductive umpolung carbonyl allylation using less expensive transition metals, e.g. nickel is still in need,[9] although it has been widely explored in the asymmetric carbonylation of alkynes, dienes and allenes .[10]

In the course of our studies of Ni-catalyzed reductive coupling of alkyl electrophiles with other electrophiles,[11] we have noticed that allylic acetates and carbonates react with aldehydes and ketones in the presence of zinc powder. Herein we disclosed our discovery of Ni-catalyzed asymmetric reductive coupling of allylic carbonates with aldehydes using zinc as the terminal reductant. Moderate to high levels of enantioselectivities were observed, which appears to be significantly effected by the substitution patterns on the allylic carbonates. To the best of knowledge, this work features the first Ni-catalyzed asymmetric reductive allylation of aldehydes with allylic carbonates. Our preliminary mechanistic studies favored that the enantioselectivities should arise from addition of the weak nucleophilic allyl-Ni to aldehydes.[12]

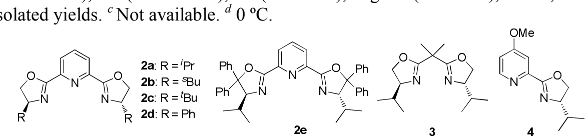
We first examined the coupling of methyl 2-phenyl allylic carbonate with 4-anisaldehyde (Table 1). After extensive screening of the reaction conditions, we identified that use of NiI_2, tridentate Pybox ligands and CuI in DMF was superior to other nickel sources, ligands, additives and solvents (entries 1–8). With a combination of NiI_2/**2c**/CuI in the presence of zinc powder at 25 ^oC, **1** was generated in 92% yield and 73% ee (entry 4). The use of $Ni(COD)_2$ further boosted the ee to 77% (entry 9). Lowering the temperature to 0 ^oC increased the ee to 86% (entry 10). $Ni(ClO_4)_2$•$6H_2O$ proved to be more effective than $Ni(COD)_2$, which generated **1** in 91% ee even at 25 ^oC; slight increase of the ee value was observed at 0 ^oC (entries 11–12). Interestingly, replacement of CuI with CsI delivered equivalent yield and ee (entry 13); without additives, 91% ee could still be attained (entry 14). Moreover, 2-phenyl allylic acetate is equally effective.

Table 1. Optimization of the reaction conditions for 1.[a]

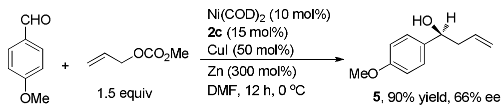


entry	Ni	ligand	additive	yield (%)[b]	ee (%)
	NiI_2	**2a**	none	90	25
2	NiI_2	**2a**	CuI (50%)	90	40
3	NiI_2	**2b**	CuI (50%)	95	35
4	NiI_2	**2c**	CuI (50%)	92	73
5	NiI_2	**2d**	CuI (50%)	95	20
6	NiI_2	**2e**	CuI (50%)	76	0
7	NiI_2	**3**	CuI (50%)	trace	NA[c]
8	NiI_2	**4**	CuI (50%)	38	0
9	$Ni(COD)_2$	**2c**	CuI (50%)	98	77
10	$Ni(COD)_2$	**2c**	CuI (50%)	95	86[d]
11	$Ni(ClO_4)_2$•$6H_2O$	**2c**	CuI (50%)	95	92[d]
12	$Ni(ClO_4)_2$•$6H_2O$	**2c**	CuI (50%)	95	91
13	$Ni(ClO_4)_2$•$6H_2O$	**2c**	CsI (50%)	95	91
14	$Ni(ClO_4)_2$•$6H_2O$	**2c**	none	95	**91**

[a] Reaction Conditions: aldehyde (100 mol%, 0.15 M in DMF), allylic carbonate (150 mol %), Zn (300 mol %), Ni (10 mol%), Ligand (15 mol%), 25 ºC, 12 h. [b] Isolated yields. [c] Not available. [d] 0 ºC.

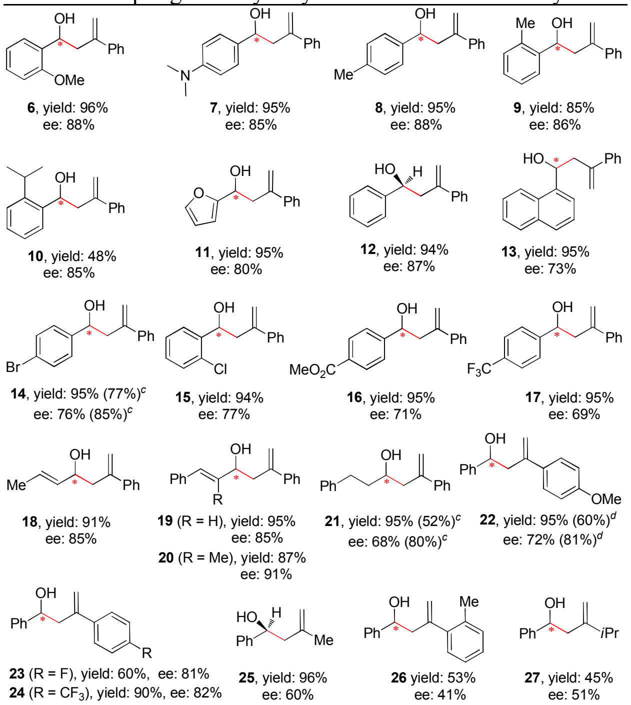


Under the optimized reaction conditions (Table 1, entry 14), the coupling of unsubstituted allylic carbonate with 4-anisaldehyde delivered **5** in 49% ee albeit in high yield. Further optimization indicated that the conditions in Table 1, entry 10 promoted the ee to 66% (Scheme 1). This result suggests that optimal enantioselectivities for the allylic carbonates bearing different substitution patterns may be achieved by modification of the optimized conditions.



Scheme 1. Optimized reaction conditions for **5**.

Table 2. Coupling of 2-aryl allylic carbonates with aldehydes.[a,b]

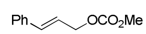
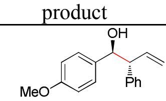
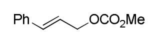
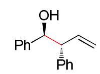
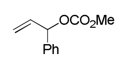
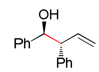
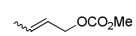
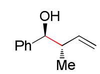
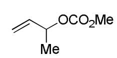
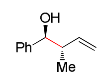


[a] Reaction Conditions: as in Table 1, entry 14. [b] Isolated yields. [c] With CsI (50 mol%) at -25 °C. [d] With CsI (50 mol%) at -15 °C.

Application of the optimized conditions (Table 1, entry 14) to the coupling of other 2-aryl allylic acetates with a variety of aldehydes was performed next (Table 2). The aromatic aldehydes that do not bear electron-withdrawing groups generally produced high ees as in **6–12**; this includes sterically hindered 2-*i*Pr-benzaldehyde. The naphthyl aldehyde produced **13** in 73% ee. The Cl- and Br-substituted benzaldehydes gave similar ees regardless of the substitution patterns as evident in **14** and **15**. On the other hand, the electron-withdrawing groups appeared to reduce the values of ees as evident in **16–17**. Cinnamaldehyde and (*E*)-but-2-enal also gave rise to the homoallylic alcohols **18–20** in high ees. Aliphatic 3-phenylpropanal delivered **21** in 68% ee. The coupling of benzaldehyde with 2-(4-methoxy), 2-(4-fluoro) and 2-(4-trifluoromethyl)phenyl allylic carbonates and 2-methyl allylic carbonate produced **22□ 25** in 72%, 81%, 82% and 60% ees, suggesting that electronic nature of the allylic partners is important in control of enantioselectivities. The sterically more hindered 2-(2-methyl)phenyl and 2-isopropyl allylic carbonates diminished ees as evident in **26** and **27**. The addition of CsI at -25 °C boosted the ee for **14** and **21** to 85% and 80%, respectively. Likewise, the ee for **22** was enhanced to 81% at -15 °C. However, lowering the temperatures for **6□8**, **11□19**, **21□22** and **25** did not resulted in better ees.

Using the optimized conditions (Table 1, entry 14) for the reductive coupling of aromatic aldehydes with 1- and 3-substituted allylic carbonates delivered the homoallylic products **28–30** in excellent yields (Table 3). Excellent anti/syn selectivities were observed for aryl-substituted allylic carbonates (Table 3, entries 1–3), whereas poor anti/syn selectivities were obtained for carbonates bearing methyl substituents (Table 3, entries 4–5). In general, the ees were moderate even when the temperature was lowered to -25 °C (Table 3, entries 2 and 3).

Table 3. Carbonyl allylation of other allylic carbonates. [a,b,c,d]

entry	substrate	product	result
1			**28** yield: 95% anti/syn: 99/1 ee: 64%
2			**29** yield%: 95 (67)[e] anti/syn: 97/3 (97/3)[e] ee%: 50 (64)[e]
3			**29** yield%: 85 (67)[e] anti/syn: 97/3 (97/3)[e] ee%: 53 (64)[e]
4	 (*E*:*Z* = 1:1)		**30** yield%: 95% anti/syn: 59/41 ee%: 60 (anti), 60 (syn)
5			**30** yield%: 95% anti/syn: 59/41 ee%: 66 (anti), 66 (syn)

[a] Reaction Conditions: as in Table 1, entry 14. [b] Isolated yields. [c] The anti/syn ratios were determined by ^{1}H NMR analysis. [d] The absolute stereochemistry is not determined. [e] The reaction was run at -25 °C.

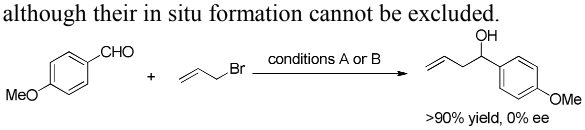
It was interesing to note that coupling of 1-phenyl allylic carbonate with benzaldehdye gave **29** with equivalent results as the 3-phenyl analog (Table 3, entries 2–3). Likewise, similar yields, drs and ees were observed for the coupling of 3-methyl- and 1-methyl allylic carbonates (Table 3, entries 4–5), supporting that the formation of Ni-π-allyl complexes is one of the key steps in the catalytic process. Low diastereoselectivities were observed for 1- or 3-methyl-subsituted allylic carbonates (Table 3, entries 4–5), indicating that a possible equilibrium between η^1-(*E*)-allyl-Ni and (*Z*)-allyl-Ni when alkyl substituents are present at C1 or C3 positions of allylic carbonates.[13]

Table 4. Coupling of 4-anisaldehyde with methyl 2-phenyl allylic carbonate generating **1** without Zn powder.

entry	Ni(COD)$_2$	ligand **2c**	additive	yield/ee
1	150 mol %	none	none	90/0
2	150 mol %	150 mol %	none	90/35
3	150 mol%	15 mol %	Ni(ClO$_4$)$_2$ (10%)	93/91
4	150 mol %	15 mol %	Zn(ClO$_4$)$_2$ (10%)	90/91
5	150 mol %	15 mol %	CsI (100%)	90/30

Transformation of the weak nucleophilic allyl-Ni intermediate into more reactive allyl-Zn is possible by reductive transmetallation of allyl-Ni with Zn or by transmetallation of allyl-Ni with Zn^{2+}.[9a,14] It is therefore important to identify whether chiral allyl-Ni(II) was capable of adding to the aldehydes.[12] The coupling of 4-anisaldehyde with 2-phenyl allylcarbonate using 1.5 equiv of Ni(COD)$_2$ in the absence of Zn and ligand generated **1** in 90% yield (Table 4, entry 1). With 1.5 equiv of ligand **2c**, 35% ee was obtained without eroding the yield. Interestingly, addition of 10% of $Ni(ClO_4)_2$ or $Zn(ClO_4)_2$ drastically increased the ees to 91%, indicating the important role of ClO_4^- (entries 3–4). The presence of 100% CsI also provided **1** with 30% ee (entry 5). These results suggest that transformation of allyl-Ni to allyl-Zn is not necessary for this coupling event.[14]

In addition, treatment of 4-anisaldehyde with allylbromide in the presence or absence of $Ni(ClO_4)_2{\bullet}6H_2O$ led to **5** in excellent yields (Scheme 2). No enantioselectivities were observed in both cases, owing to in situ formation of allyl-zinc reagents that react with aldehyde through a Barbier mechanism.[15] As a result, we reason that in our Ni-catalyzed reductive coupling process, the enantioselectivity should not arise from allyl-zinc reagents, although their in situ formation cannot be excluded.



Conditions A: $Ni(ClO_4)_2{\bullet}6H_2O$ (10 mol %), **2c** (15 mol %), Zn (300 mol %), DMF, rt. Conditions B: **2c** (15 mol %), Zn (300 mol %), DMF, rt.

Scheme 2. Coupling of allylbromide with 4-anisaldehyde

In summary, we have disclosed asymmetric Ni-catalyzed reductive coupling of allylic carbonates with aldehydes utilizing zinc powder as the terminal reductant. The reaction conditions are particularly effective for the 2-aryl-allylic carbonates which generate the homoallylic alcohols in good to excellent ees for both aromatic and aliphatic aldehydes. The preliminary studies suggest that the enantioselectivity arises from addition of allyl-Ni to aldehydes rather than the more reactive allyl-Zn that may be produced in the reactions.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Charaterization of all new compounds and HPLC data for ees. See DOI: 10.1039/b000000x/

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