Et_2Zn as a base: zinc enolate free from other metals significantly enhances the enantiomeric excess in palladium-catalyzed allylic alkylation

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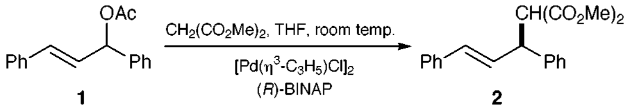
The enantiomeric excess of palladium-catalyzed allylic alkylations was greatly increased when Et_2Zn was used as the base to generate an anion from malonates.

Et_2Zn is a widely used nucleophilic agent. Examples include the ethylation of aldehydes,[1] 1,4-addition to α,β-unsaturated carbonyl compounds,[2] preparation of the Simmons-Smith reagent[3] and the umpolung reaction of π-allylpalladium.[4] Furthermore, Et_2Zn is known to be a weak Lewis acid to which oxygen, nitrogen and halogens can coordinate.[5] To the best of our knowledge, it has not been used as a base to generate zinc enolates. These are routinely generated *in situ* by metal–metal exchange with other metal enolates. Since the other metal coexists together with zinc in the reaction medium, it is obvious that the aggregation state is quite different from that of zinc enolates free from other metals, which may affect the stereochemical outcome of the reactions. We report here a remarkable enhancement of the enantiomeric excess (ee) in a palladium-catalyzed allylic alkylation using zinc enolates free from other metals, generated with Et_2Zn as a base.

We have chosen the reaction shown in Scheme 1 as a standard reaction to evaluate the effect of zinc enolates free from other metals.[6] Et_2Zn is known to be basic enough to form a zinc alkoxide when it is mixed with an alcohol.[7] Based on the pK_a values of alcohols and the malonate, we can expect that a hydrogen of the active methylene group of dimethyl malonate will be removed by Et_2Zn. A popular chiral ligand, (*R*)-BINAP, was used for the reaction and the results are listed in Table 1. A zinc enolate prepared by metal exchange from the corresponding sodium enolate showed a considerable increase in ee, although the reactivity decreased (entries 2 and 3). A significant difference in ee was not observed between the lithium enolates and the zinc enolates generated by exchange from the lithium enolates (entries 5–8). A remarkable increase in ee was observed when the zinc enolate that was directly generated with Et_2Zn was used (entry 9). These findings indicate that the aggregation state of the zinc malonate prepared with Et_2Zn is different from that prepared by metal exchange, although it is premature to present an explanation for the increase in enantioselectivity with zinc enolate free from other metals. Temperature affects the reaction rate, but not the ee, when zinc enolate free from other metals is used (entries 9–11).



Scheme 1

Table 1 Effect of counter cation on the allylic alkylation of the racemic acetate **1** catalyzed by the Pd^0–(*R*)-BINAP giving (*S*)-**2**[a]

Entry	Base	Additive[b]	*t*/h	Yield (%)	Ee (%)
1	KH	none	5	77	59
2	NaH	none	18	75	35[c]
3	NaH	$ZnCl_2$	48	19 (58)[d]	57
4	LiH	none	64	68 (89)[d]	72
5	LDA	none	2	87	76
6	LDA	$ZnCl_2$	68	60 (71)[d]	87
7	BuLi	none	24	91	56
8	BuLi	$ZnCl_2$	42	19	53
9	$ZnEt_2$	none	39[e]	46 (72)[d]	98
10	$ZnEt_2$	none	20	84	99
11	$ZnEt_2$	none	0.5[f]	89	97
12	$ZnEt_2$	LiCl	42	67	82

[a] Reaction conditions: Allylic acetate **1** (1 equiv.), dimethyl malonate (2 equiv.), base (2 equiv.), (*R*)-BINAP (8 mol%), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol%) in THF at room temperature. [b] 2 equiv. [c] A 30% ee was reported under similar conditions (See ref. 8). [d] Yield in parenthesis based on the consumed starting material. [e] At 0 °C. [f] At reflux temperature.

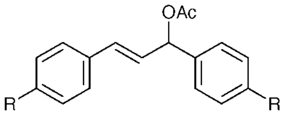
The results of allylic alkylations with various nucleophiles are listed in Table 2. Zinc enolates generally gave ees greater than those with sodium enolates at room temperature. Zinc enolates generated from malonic acid derivatives again gave comparable ees at various temperatures (entries 1,2 and 10, 11), but the ee decreased markedly at higher temperature with other enolates (entries 4, 5 and 7, 8).

Remarkably high ees were observed in the alkylation of other allylic acetates **3–5** and **9** with the zinc malonate (Table 3). The

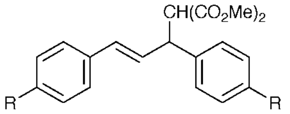
Table 2 Allylic alkylation of the racemic acetate **1** with various nucleophiles catalyzed by the Pd^0–(*R*)-BINAP

Entry	Nucleophile	Base	*T*/°C	*t*/h	Yield (%)	Ee (%)
1	$CH_2(CO_2CH_2Ph)_2$	$ZnEt_2$	20	20	81	92
2	$CH_2(CO_2CH_2Ph)_2$	$ZnEt_2$	66[a]	1	78	95
3	$CH_2(CO_2CH_2Ph)_2$	NaH	20	2	83	0
4	$CH_2(CN)_2$	$ZnEt_2$	20	48	48	85
5	$CH_2(CN)_2$	$ZnEt_2$	66[a]	1.5	89	7
6	$CH_2(CN)_2$	NaH	20	48	33 (62)[b]	75
7	$CH_2(SO_2Ph)_2$	$ZnEt_2$	20	72	24 (44)[b]	92
8	$CH_2(SO_2Ph)_2$	$ZnEt_2$	66[a]	2	70	39
9	$CH_2(SO_2Ph)_2$	NaH	20	45	36 (60)[b]	88
10	$PhCH_2CH(CO_2Me)_2$	$ZnEt_2$	20	168	47 (53)[b]	70
11	$PhCH_2CH(CO_2Me)_2$	$ZnEt_2$	66[a]	3	92	76
12[c]	$PhCH_2CH(CO_2Me)_2$	NaH	25	211	45	0

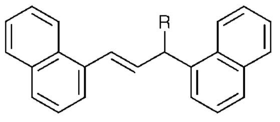
[a] Reflux in THF. [b] Yield in parenthesis based on the consumed starting material. [c] Taken from the ref. 8.



3 R = Cl
4 R = Br
5 R = Me



6 R = Cl
7 R = Br
8 R = Me



9 R = OAc
10 R = $CH(CO_2Me)_2$

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Table 3 Allylic alkylation of the racemic acetates **3**–**5** and **9** with dimethyl malonate catalyzed by Pd^0–(*R*)-BINAP

Entry	Compound	Base	*T*/°C	*t*/h	Product	Yield (%)	Ee (%)
1	**3**	$ZnEt_2$	20	20	**6**	92	97
2	**3**	$ZnEt_2$	66[a]	0.5	**6**	95	96
3	**3**	NaH	20	4	**6**	88	30
4	**4**	$ZnEt_2$	20	40	**7**	60 (65)[b]	97
5	**4**	$ZnEt_2$	66[a]	1	**7**	40	97
6	**4**	NaH	20	4	**7**	90	34
7	**5**	$ZnEt_2$	20	72	**8**	73	78
8	**5**	$ZnEt_2$	66[a]	1	**8**	91	80
9	**5**	NaH	20	4	**8**	78	19
10	**9**	$ZnEt_2$	20	48	**10**	73	88
11	**9**	$ZnEt_2$	66[a]	2	**10**	95	90
12	**9**	NaH	25	8	**10**	88	67

[a] Reflux in THF. [b] Yield in parenthesis based on the consumed starting material.

general tendency of zinc malonates described previously is observed in these cases. Thus, the zinc enolate gives greater ee than the sodium enolate and ees are not affected by differences in temperature.

In conclusion, we found that zinc malonates free from other metals can give high ees in allylic alkylations catalyzed by a palladium–(*R*)-BINAP complex. The present results suggest that zinc enolates free of other metals may be used to increase ees and/or chemical yields in other types of reactions involving enolates, although this application would be limited to highly acidic compounds.[9]

Notes and references

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