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Asymmetric Allylic Alkylation of Alkanoic-Acid Ester Enolates

Robin Visse,[a] Martin-Alexander Möllemann,[a] and Manfred Braun*[a]

Dedicated to Professor Hans-Ulrich Reißig on the occasion of his 70th birthday

Abstract: A protocol for the direct palladium-catalyzed asymmetric allylic alkylation of simple alkanoic-acid esters through their lithium enolates has been developed. The method permits to create stereogenic centers in the homo-allylic or allylic position. The configuration of the allylation products has been elucidated.

Introduction

The palladium-catalyzed asymmetric allylic alkylation, known as 'Tsuji–Trost reaction' has developed into a highly efficient and versatile method for enantioselective carbon–carbon bond formation.[1] For a long period, the reaction suffered however from a limitation: It was restricted to stabilizes carbanions that function as "soft" carbon nucleophiles. Guided by the idea that the scope of the Tsuji-Trost reaction will be enhanced considerably if it can be extended to nonstabilized, preformed enolates[2] as nucleophiles, protocols for palladium- and iridium-catalyzed asymmetric allylic alkylations of ketones through their tin, silicon, magnesium and lithium enolates were elaborated since the beginning of the 2000s.[3] These procedures were completed by decarboxylative variants that started from enol carbonates or β-keto-esters and permitted enantioselective allylic alkylations as well.[4] Several carboxylic-acid derivatives like amides[5] and lactones[6] were successfully submitted to asymmetric allylic alkylations through their preformed enolates, and lactams were allylated using the asymmetric decarboxylative protocol.[7] Even doubly deprotonated carboxylic acids have been shown to function as suitable nucleophiles for stereoselective palladium-catalyzed allylic alkylations.[8]

Among all the preformed enolates, those derived from carboxylic esters are known as the most fragile and sensitive ones, particularly due to their inherent tendency to decompose under formation of ketene and alkoxide. Therefore, it is not surprising that ester enolates were used as nucleophiles in Tsuji-Trost reactions only reluctantly. So far, the only broadly applicable protocols are based on chelated zinc enolates derived from α-amino acids or peptides ('Kazmaier enolates').[9] Whereas several ester enolate equivalents like N-acyloxazolinones and 2-acylimidazoles were applied in decarboxylative asymmetric allylic alkylations,[10] the direct stereoselective allylic alkylation of nonchelated enolates of simple alkanoic-acid esters has not been disclosed so far. In this article, we describe our studies aimed at palladium-catalyzed enantioselective allylic alkylations of lithium enolates of carboxylic esters (Figure 1).

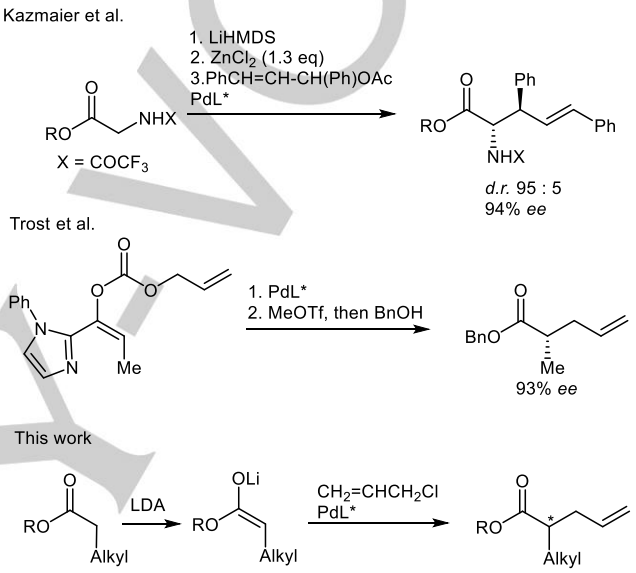

Figure 1. Asymmetric allylic alkylations of esters and ester surrogates..

Results and Discussion

Prerequisite to any stereoselective α-functionalization of alkanoic esters is the formation of the enolate in the desired configuration: *cis* and *trans*.[11] Fortunately, the seminal contributions of Ireland and co-workers opened controlled routes to generate either diastereomer by means of suitable reaction conditions.[12] The selectivity in enolate formation depends however on the particular α-substituent.[2] For evaluating the asymmetric allylic alkylation of ester enolates, we have chosen methyl 3,3-dimethylbutyrate (**1a**) that is known to form the *trans*-enolate in a highly selective manner (*trans*-**2a**:*cis*-**2b** = 97:3). In previous studies on palladium-catalyzed reactions of allylic carbonates with "hard" nucleophiles, we noticed that the presence of lithium chloride was crucial to both reactivity and enantioselectivity. Therefore, we had used the salt as an additive to the reaction mixture. Feeling that using the salt in over-stoichiometric amounts is rather uneconomical, we turned to allylic chlorides **3** as a source for lithium chloride that forms gradually as the reaction proceeds.

Thus, carboxylic ester **1a** was deprotonated with LDA in THF and the enolate mixture of *trans*-**2a** and *cis*-**2b** (97:3) was allowed to react with allyl chloride (**3a**) in the presence of the catalyst precursor tris(dibenzylideneacetone)dipalladium-

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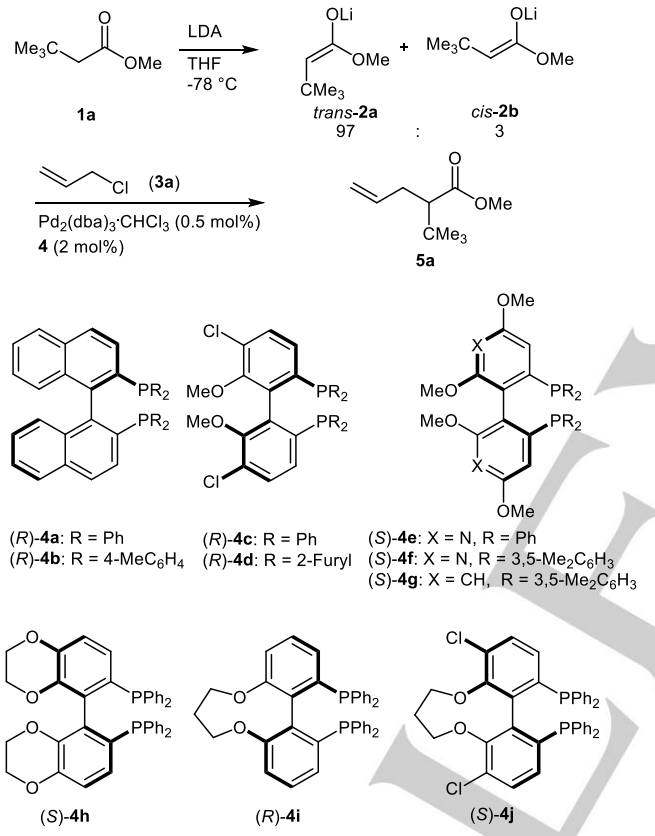
chloroform adduct and the ligands **4a**-**j** (Scheme 1). We had noticed previously that, in asymmetric allylation reactions of ketone and lactone enolates, only axially-chiral biaryl-derived bisphosphanes provided a significant degree of enantioselectivity. As a consequence, this type of ligands was used for optimizing the allylation of ester **1a**. The palladium-catalyzed reaction was performed at –78 °C. In control experiments, we had proved that in the absence of the noble metal no reaction between the enolate and allyl chloride occurred. The results of the optimization study, yields of the allylated ester **5a**, isolated by column chromatography, and enantiomeric excess determined by chiral GC are shown in Table 1.



Scheme 1. Enantioselective palladium-catalyzed allylic alkylation of carboxylic ester **1a** mediated by ligands **4a**-**j**.

The standard ligand (*R*)-BINAP (**4a**) (entry 1), the Cl-MeO-BIPHEP-type ligands **4c** and **4d** (entries 3 and 4) as well as the PHOS-type ligands **4e** and **4f** (entries 5 and 6) and SYNPHOS (**4h**) (entry 8) led to substantial, but not satisfying enantioselectivities in the range of 70% *ee*. Remarkably, the extension of the aryl groups at the phosphorus atom, realized by tolyl-BINAP (**4b**) and xylyl-GARPHOS (**4g**) proved itself to be deleterious and resulted in very moderate *ee*-values (entries 2 and 7). Optimum results however were obtained with Zhang's C_3-TUNEPHOS (**4i**)[13a] and the bis-chloro-substituted analogue **4j** developed recently by us.[13b] With these ligands, enantioselectivity reached 80% *ee* (entries 9 and 10) that could further enhanced by lowering the reaction temperature to –100 °C, without loss in the chemical yield.

Table 1. Optimization of the reaction conditions

Entry	Ligand	Allylation product **5a** Configuration	Yield [%][a]	*ee* [%]
1	(*R*)-**4a**	(*R*)-**5a**	54	70
2	(*R*)-**4b**	(*R*)-**5a**	67	43
3	(*R*)-**4c**	(*R*)-**5a**	78	73
4	(*R*)-**4d**	(*R*)-**5a**	54	67
5	(*S*)-**4e**	(*S*)-**5a**	68	69
6	(*S*)-**4f**	(*S*)-**5a**	66	75
7	(*S*)-**4g**	(*S*)-**5a**	57	30
8	(*S*)-**4h**	(*S*)-**5a**	76	68
9	(*R*)-**4i**	(*R*)-**5a**	73	79
10	(*S*)-**4j**	(*S*)-**5a**	83	80
11	(*R*)-**4i**	(*R*)-**5a**[b]	85	88
12	(*S*)-**4j**	(*S*)-**5a**[b]	83	85

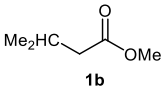
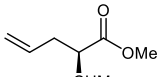
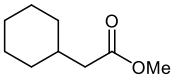
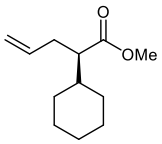
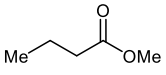
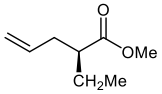
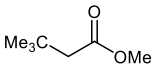
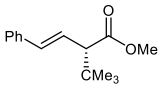
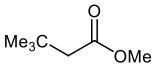
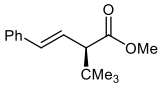
[a] Isolated yield. [b] Reaction temperature: –100 °C.

Having evaluated the ether-bridged TUNEPHOS-type ligands **4i** and **4j** as the most efficient ones for catalyzing the allylic alkylation of methyl 3,3,-dimethybutyrate (**1a**), alkanoic esters **1b**-**d** were submitted to the same protocol. The results are shown in Table 2. Under those deprotonation conditions, a high preference for the formation of *trans*-enolates has been proved or assumed based upon analogy.[14] The α-isopropyl- and α-cyclohexyl-substituted esters **1b** and **1c** led to the formation of allylation products **5b** and **5c**, respectively in remarkable enantiomeric excess. On the other hand, the result with methyl butyrate **1d** is poor and the alkene **5d** was formed in 30% *ee* only. The protocol was also extended to cinnamyl chloride (**3b**) as allylic component. In this case, a fair degree of enantioselectivity in the formation of products (*S*)-**5e** and (*R*)-**5e** was reached by using the ligands (*S*)-**4j** or (*R*)-**4i**, respectively. The low isolated chemical yields of allylation products **5b** and **5d** are caused mainly by their volatility that led to loss of material upon the isolation.

We did not use *cis*-enolates for two reasons: Ireland's studies[12] had shown that the selectivity for them is only moderate (**2a**:**2b** = 9:91, and even lower for other alkanoic ester enolates). Furthermore, the formation of *cis*-ester enolates requires HMPA or DMPU. Both are deleterious to the selectivity in our allylation protocol, as they disrupt the aggregate of lithium enolate, lithium chloride and allylpalladium, an arrangement that was postulated

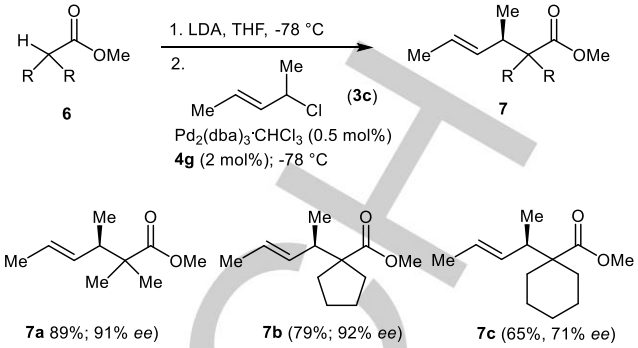
to be responsible for high stereoselectivity in the allylation step.[6]

Table 2. Scope of the enantioselective allylic alkylation of α-substituted carboxylic esters **1**.

Alkanoic Ester **1**	Ligand	Allylation Product **5**	Yield [%][a]	*ee* [%]
 **1b**	(*R*)-**4i**	 (*R*)-**5b**	50	81
 **1c**	(*R*)-**4i**	 (*R*)-**5c**	90	91
 **1d**	(*R*)-**4i**	 (*S*)-**5d**	50	30
 **1a**	(*S*)-**4j**	 (*S*)-**5e**	86[b]	79
 **1a**	(*R*)-**4i**	 (*R*)-**5e**	79[b]	75

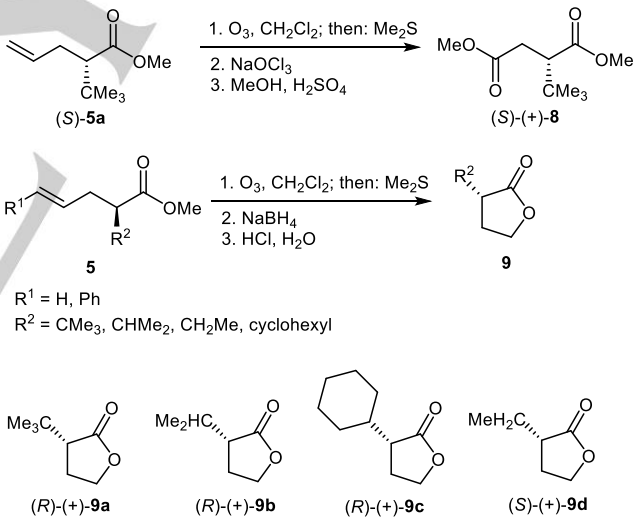
[a]) Isolated yield. [b] Allylation reagent: (*E*)-PhCH=CHCH$_2$Cl (**4b**)

After the protocol reported has been found to be appropriate for introducing a stereogenic center in the homoallylic position, we were interested whether the procedure is also suitable to create an allylic stereocenter in an enantioselective manner. For this purpose, we submitted α,α-disubstituted carboxylic esters **6a**-**c** to the palladium catalyzed reaction with dimethylallyl chloride (**3c**). When, however, catalyzed by TUNEPHOS ligands **4i** or **4j**, the reaction occurred in an unsatisfying manner in terms of chemical yield and enantioselectivity, indicating that this type of ligands is unsuitable for 1,3-disubstituted allyl palladium complexes. Fortunately, (S)-xylyl-GARPHOS (**4g**) proved itself as much more efficient and catalyzed the formation of the allylation products **7** in fair to high enantioselectivity, as shown in Scheme 2.



Scheme 2. Enantioselective formation of α,α-disubstituted carboxylic esters **7**.

As the absolute configuration of the allylation products **5a**-**5e** was unknown, it was determined unambiguously by chemical correlation. First, pentenoic ester **5a**, obtained in 70% *ee* by allylic alkylation with the ligand (*S*)-**4j**, was submitted to an ozonolysis, followed by oxidation with sodium chlorate and subsequent esterification. The comparison of the optical rotation of succinate (+)-**8** with the data described in the literature[15] revealed the compound (+)-**8** and, consequently, the allylation product (+)-**5a** to be (*S*)-configured (Scheme 3).



Scheme 3. Conversion of carboxylic esters **5** into succinate **8** and lactones **9** for determination of the absolute configuration.

Furthermore, all the carboxylic esters **5a**-**5e**, obtained by the allylation protocol with (*R*)-configured ligands **4** were converted into γ-butyrolactones **9a**-**d** by ozonolysis followed by reduction and cyclization under acidic conditions. Lactones (*S*)-(–)-**9b** and (R)-(–)-**9d** have been described in the literature.[16] Positive sign of optical rotation was observed for lactones **9b** and **9d** that resulted from allylation products **5b** and **5d**, both prepared with ligand (*R*)-**3i** (see Table 1) Thus, the configurations were assigned as (*R*)-(+)-**9b** and (S)-(+)-**9d** to the lactones and,

based thereupon, (*R*)-(–)-**5b** and (*S*)-(–)-**5d** to the allylated esters (Scheme 3).[17] In order to confirm the homo-chirality of all the carboxylic esters obtained with (*R*)-configured ligands **4**, the CD spectra of the corresponding lactones were measured and displayed the same sign of Cotton effects (see Supporting Information). The configuration of carboxylic esters **7a**-**7c** carrying the stereogenic center in the allylic position was assigned to be *R* by analogy to the stereochemical outcome observed with lactone enolates.[6a]

Conclusions

In summary, we have elaborated a protocol that enables a palladium-catalyzed asymmetric allylic alkylation of lithium enolates derived from simple alkanoic-acid esters. This direct method can be considered an alternative to detours that are based on ester surrogates. The protocol permits to create stereogenic centers in the homo-allylic or allylic position, depending on the substrates chosen. The configuration of the allylation products was elucidated.

Experimental Section

General procedure for the allylic alkylation of alkanoic esters 1 and 6:

A dry 100-mL two-necked flask, equipped with a magnetic stirrer, was charged with $[Pd_2(dba)_3]{\cdot}CHCl_3$ (12.5 mg; 12.4 µmol) and 50 µmol of the corresponding ligand **4**. The flask was closed with a septum, connected to a combined nitrogen/vacuum line, evacuated and filled with nitrogen. Then, dry THF (20 mL) was added by syringe. After chloride **3** (5.5 mmol) had been injected, the resulting solution rapidly turned yellow and was cooled down to –78 ºC.

A second 100 mL two-necked flask with a connection to the combined nitrogen/vacuum line was equipped with a magnetic stirrer and a resistance low-temperature thermometer (introduced through a septum). The flask was three times evacuated and refilled with nitrogen. Into this flask, diisopropylamine (0.71 mL, 5.0 mmol) and dry THF (5 mL) were injected. After cooling to –78 °C, *n*-butyllithium (1.6 M in *n*-hexane, 3.1 mL, 5.0 mmol) was added dropwise by syringe; at such a rate that the temperature did not exceed –70 °C. After stirring at 0 °C for 30 min, the mixture was cooled to -78 °C and the corresponding ester **1** or **6** (5.0 mmol) was injected by syringe. Stirring was continued at –78 °C for 1 h.

The solution in the first flask was transferred into the second flask by means of a cannula while maintaining a slight nitrogen overpressure in the first flask, whereas the second one was slightly evacuated. After the combination of the two mixtures had been completed at –78 °C, stirring was continued at the same temperature for 24. Then, the mixture was poured into a saturated aqueous solution of ammonium chloride and extracted with diethyl ether (three 20-mL portions). The combined organic layers were dried with magnesium sulfate, and the solvent was removed in a rotary evaporator. The crude product was purified by column chromatography or fractional distillation.

Analytical and spectroscopic data, copies of NMR spectra and chiral chromatograms of the compounds prepared as well as procedures for the preparation of succinate **8** and lactones **9** are given in the Supporting Information.

Acknowledgments

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Keywords: Catalysis • Enantioselectivity • Lithium •Palladium • Synthetic methods.

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[17] Within the homochiral series **5** and **9**, the inversion of configuration for **5d** and **9d** is a formal one, due to priority change of the substituents at the stereogenic center.

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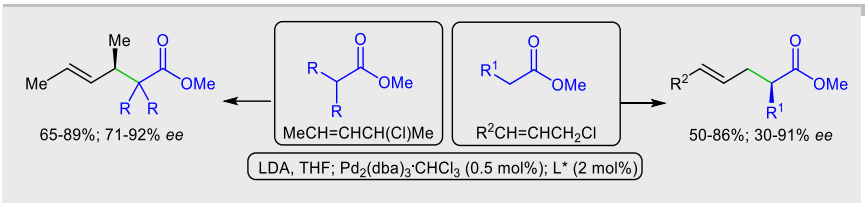

Lithium - Palladium

*Robin Visse, Martin-Alexander Möllemann, Manfred Braun**

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Asymmetric Allylic Alkylation of Alkanoic-Acid Ester Enolates

The palladium-catalyzed enantioselective allylic alkylation of nonstabilized lithium enolates is a long-standing problem in asymmetric syntheses. A protocol based upon suitable reaction conditions and appropriate ligands enables the asymmetric allylation of alkanoic-acid esters through their lithium enolates in a direct manner that does not require detours via ester surrogates. Thus, stereogenic centers can be created either in allylic or homo-allylic position.