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Palladium-catalyzed benzylic-like nucleophilic substitution of benzofuran-, benzothiophene- and indole-based substrates by dimethyl malonate anion

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Dedicated to Professor J.P. Genêt on the occasion of his 60th birthday

Abstract

The palladium-catalyzed benzylic-like nucleophilic substitution of acetates derived from benzofuran, benzothiophene and indole was investigated. The asymmetric substitution on racemic 1-(2-benzofuryl)ethyl acetate gave disappointing results, but the substitution product was obtained in 98% ee from (*S*)-1-(2-benzofuryl)ethyl acetate with overall retention of configuration.

Keywords: Palladium; Benzylic-like nucleophilic substitution; C–C bond formation; Benzofuran; Benzothiophene; Indole

1. Introduction

We recently described the formation of benzylic carbon–carbon [1–5], carbon–hydrogen [6,7] and carbon–nitrogen [8] bonds by palladium-catalyzed nucleophilic substitution of esters with fused six-membered aromatic rings like naphthalene (**1**), phenanthrene (**2**), quinoline (**3**) and isoquinoline (**4**) (Scheme 1). Optically active substitution products were obtained from enantiopure substrates in the presence of an achiral catalyst [2,5] or by asymmetric catalysis from racemic esters [3,5].

We postulated for this substitution a mechanism involving a cationic η^3-benzylic palladium complex **5** as depicted for the formation of **6** from 2-naphthylmethyl acetate (**1a**) (Scheme 2). The inertness of benzyl acetate under the same reaction conditions strongly support the analogy with the Tsuji–Trost reaction. If we consider the resonance energies of benzene and naphthalene (152 and 255 kJ mol^{-1}, respectively [9]), the formation of the η^3-benzylpalladium in the first step of this transformation requiring partial lost of aromatic stabilisation is less favorable for complex **7** than for its naphthylmethyl counterpart **5**.

Furan is an heteroaromatic compound with a weak resonance energy (67 kJ mol^{-1} [9]), so we expected that furylmethanol derivatives could behave as compounds **1**–**4**. But furylmethyl methyl carbonate **8** gave only a low yield ($<25\%$) of substitution product **9**, the major pathway being a degradation of the substrate in the reaction conditions (Scheme 3) [10].

We report in this article that introduction of an additionnal benzenic ring (as for naphthylmethyl compounds compared to benzyl substrates) allows the extension of the palladium-catalyzed benzylic nucleophilic substitution reaction to derivatives of benzofuran and to a lesser extent benzothiophene and indole. Some preliminary experiments were also carried out in order to obtain an enantiomerically enriched compound including a benzofuran moiety.

It should be noticed that to our knowledge a single example of this type of transformation was reported in the literature albeit in low yield in the synthesis of

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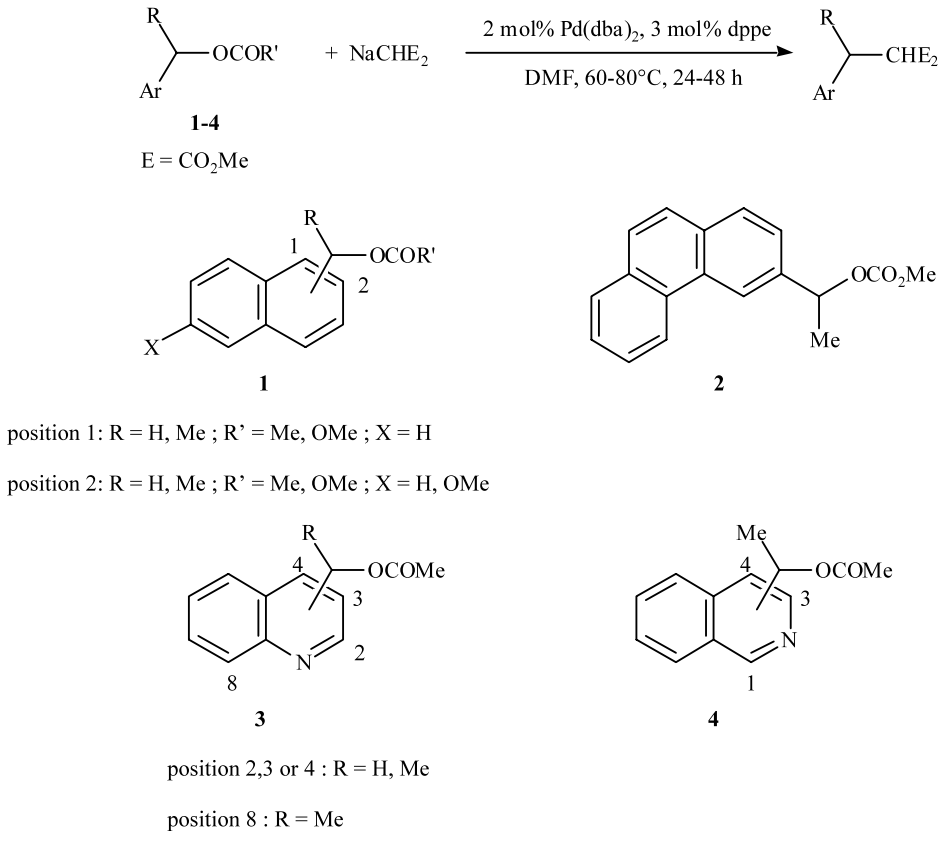
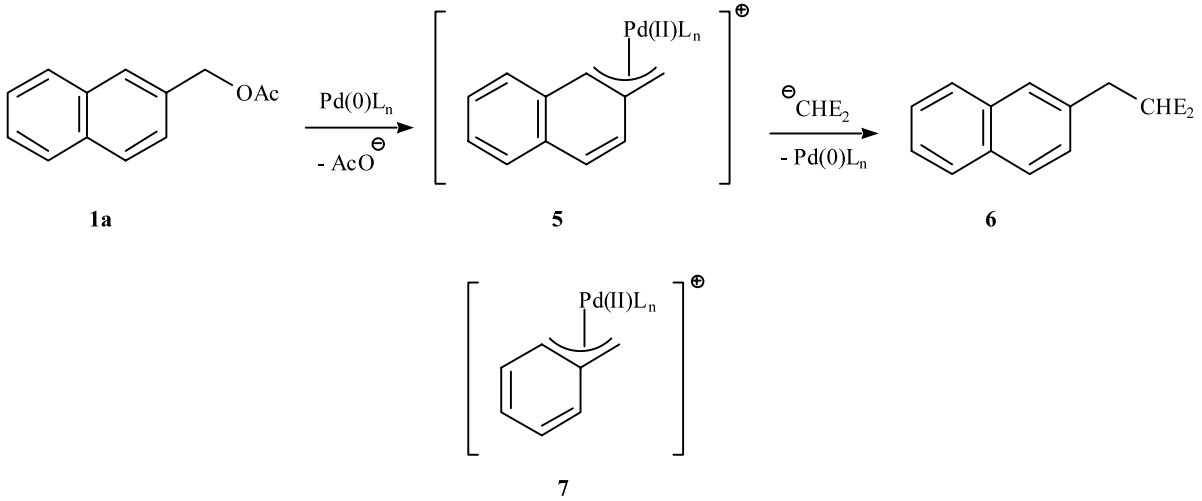


Scheme 1. Palladium-catalyzed nucleophilic substitution of fused six-membered aromatic ring substrates.



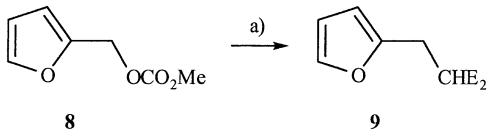
Scheme 2. Mechanism of palladium-catalyzed benzylic substitution.

inverto-yuehchuene using a *N*-protected indolylzinc chloride as nucleophile [11].

2. Preparation of the substrates

The benzofuran derivatives **10a** and **11** were obtained by a Sonogashira coupling between 2-iodophenol and propynol and but-3-yn-2-ol respectively, followed by in situ cyclization [12]. The intermediate alcohols were directly treated by acetic anhydride in the presence of LiCl [13] to give acetates **10a** and **11** (Scheme 4). Enantiomerically pure (*S*)-**11** was obtained from (*S*)-but-3-yn-2-ol in comparable yield.

By using the same procedure, 4-chloro-2-bromophenol gave compound **10b** in only 15% yield, probably due



8 9

Scheme 3. Attempted palladium-catalyzed substitution of carbonate **7**. (a) Two equivalents of $NaCHE_2$, 2 mol% $Pd(dba)_2$, 3 mol% dppe, DMF, 80 °C, 24 h (< 25%).

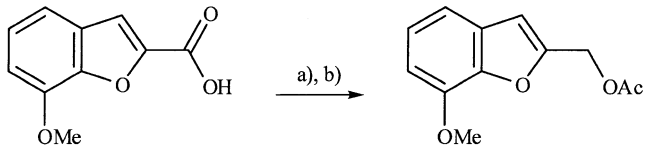
to a more difficult oxidative addition of palladium onto the bromide compared to iodide. At higher (100 °C) temperature and higher (10 mol%) catalyst loading, **10b** was obtained in a moderate 34% yield.

10c was obtained from the borane reduction followed by acetylation of commercially available 7-methoxy-2-benzofurancarboxylic acid (Scheme 5).

As described for benzofuran [14], lithiation of benzothiophene, which occurred on 2 position [15], followed by addition of DMF gave 2-benzothiophenecarboxaldelyde in good yield (Scheme 6). Reduction by sodium borohydride or reaction with methyl Grignard reagent afforded after acetylation **12** and **13**, respectively.

Esterification by diazomethane followed by LAH reduction of commercially available 2-indolecarboxylic acid afforded 2-hydroxymethylindole in good yield [16]. Acetylation was attempted as above (Ac_2O in presence of catalytic LiCl) but a very low yield of acetate **14a** was obtained, so we turned back to more classical conditions (Ac_2O, Et_3N, catalytic DMAP). With one equivalent of acetylating reagent, an inseparable mixture of unreacted alcohol, expected **14a** and diacetyled **14b** was obtained in a 24:54:22 ratio from ^{1}H-NMR spectrum. An excess of acetic anhydride cleanly produced **14b** (Scheme 7).

N-Methyl derivatives **14c** and **14d** were obtained by reduction/esterification of commercial *N*-methylindolecarboxaldehyde (Scheme 8).



10c (57%)

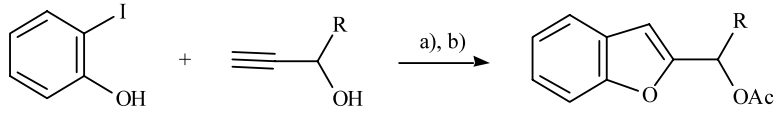
Scheme 5. Preparation of 2-(7-methoxy)benzofurylmethyl acetate **10c**. (a) BH_3.THF, THF, 20 °C. (b) Ac_2O (excess), LiCl (0.1 equivalents), 20 °C.

3. Palladium-catalyzed substitution reaction of esters 10–14

We first performed the palladium-catalyzed reaction of acetate **10a** under the conditions which were optimal on naphthalene-derived substrates [2] (Scheme 9). We observed that beside the expected substitution product **15a**, a substantial amount of disubstitution compound **16** was produced. This double alkylation of a malonate nucleophile was never observed on naphthalene substrates but have some precedent in π-allylpalladium chemistry [17,18]. However this behaviour is quite surprising in the presence of an excess amount of nucleophile as under our conditions. With less than two equivalents of nucleophile, a total conversion of acetate **10a** could not be obtained even after 48 h of reaction.

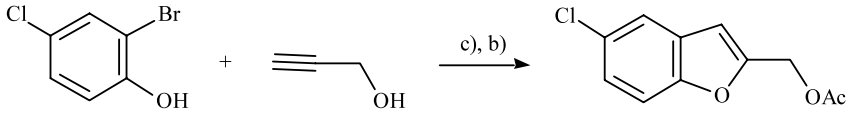
The ratio of the two products **15a** and **16** was determined from ^{1}H-NMR spectrum. The selectivity in favour of product **15a** was slightly higher in THF than in DMF. The reaction was complete in less than 4 h: the reactivity of **10a** is higher than naphthalene [1,2], quinoline and isoquinoline-based [4] substrates which required at least 24 h for total conversion.

Compounds **15a** and **16** were difficult to separate (R_f values of 0.52 and 0.62, respectively, eluent heptane/



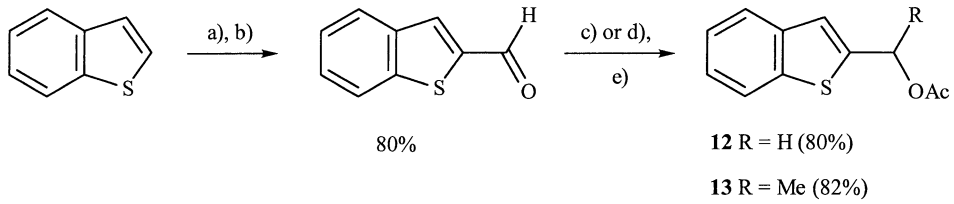
10a R = H (70%)

11 R = Me (racemic : 58%; (*S*) : 67%)



10b (34%)

Scheme 4. Preparation of benzofuran substrates **10a**–**b** and **11** by Sonogashira coupling. (a) 3 mol% $Pd(PPh_3)_2Cl_2$, 4 mol% CuI, Et_3N, DMF, 60 °C. (b) Ac_2O (excess), LiCl (0.1 equivalents), 20 °C. (c) 10 mol% $Pd(PPh_3)_2Cl_2$, 4 mol% CuI, Et_3N, DMF, 100 °C.



Scheme 6. Preparation of benzothiophene substrates **12** and **13** via lithiation. (a) *n*-BuLi, THF, 0 °C. (b) DMF (three equivalents), 20 °C. (c) for **12**: $NaBH_4$, MeOH, 20 °C. (d) For **13**: MeMgBr (1.1 equivalents), Et_2O, 0 °C. (e) Ac_2O (excess), LiCl (0.1 equivalents), 20 °C.

AcOEt 80:20). After careful flash-chromatography, **15a** could be isolated in only 37% yield.

The formation of compound **16** involved the following steps: (i) palladium-catalyzed substitution on **10a** producing **15a** via intermediate **17** (Scheme 9); (ii) acid–base exchange between **15a** and sodium dimethyl malonate; (iii) second substitution reaction involving nucleophilic attack of the conjugated base of **15a** on complex **17**.

One of the factors which governs the selectivity of the reaction is undoubtedly the position of the equilibrium between **15a** and its conjugated base. Therefore, we studied the influence of the initial malonate/deprotonated malonate ratio: the nucleophile was prepared by adding n mmol of dimethyl malonate on a suspension of NaH (2 mmol) in THF. The substitution reaction was conducted on 1 mmol of substrate **10a** (Table 1).

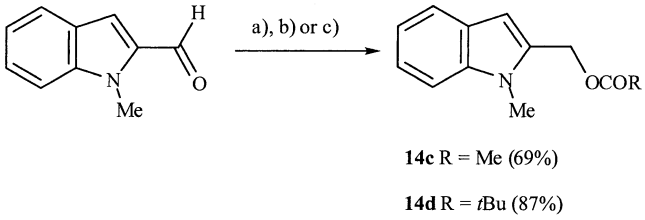
As expected, an increasing amount of dimethyl malonate in the reaction medium induced a better selectivity in favor of **15a**, since the equilibrium (ii) was shifted towards the left. The concentration of the conjugated base of **15a** was lowered and reaction producing **16** slowed down.

The above proportions were determined by ^{1}H-NMR, so there is no significant difference between the use of four and six equivalents of dimethyl malonate. In order to avoid the presence of a too large excess of dimethyl malonate at the end of the reaction (which could be detrimental to the isolation of product **15a**), we chose to conduct the reactions with four equivalents in the following.

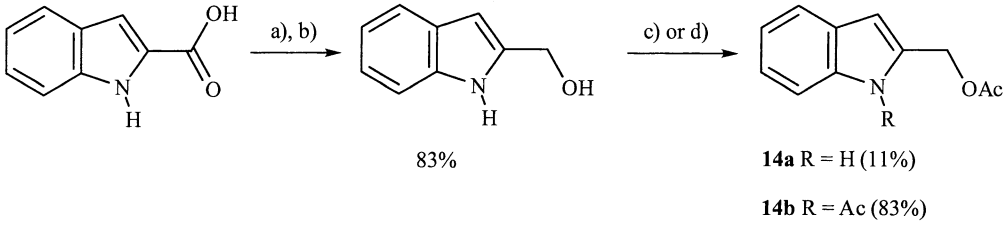
The influence of the counter ion was also briefly studied, the ratio **15a/16** could not be increased, since it was 83/17 and 90/10, respectively, using potassium *t*-butanoate and *n*-butyllithium as bases instead of sodium hydride for the deprotonation of dimethyl malonate.

On the other hand, compound **16** was isolated in 41% yield from the palladium-catalyzed reaction of the conjugated base of **15a** (two equivalents) with acetate **10a**.

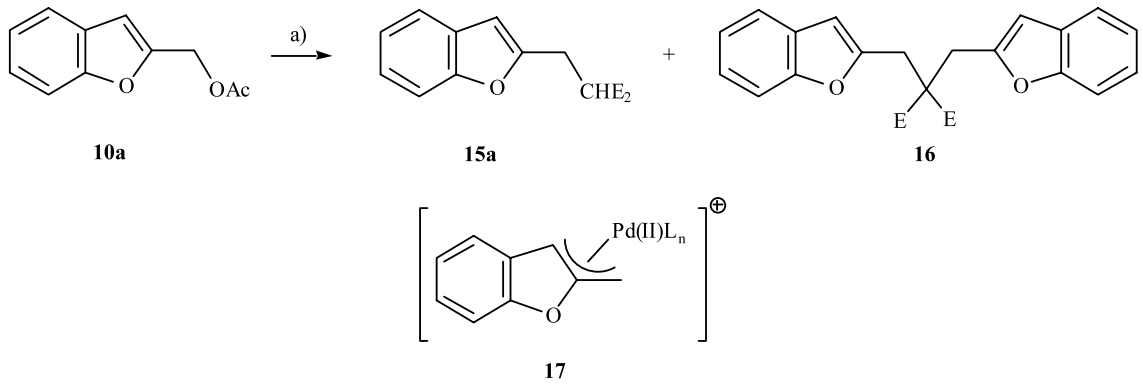
The reaction conditions determined above were applied to the other primary substrates. Benzofurans **10b** and **10c** were both less reactive than unsubstituted **10a** (Scheme 10). After 48 h, the conversion was only 67% for **10b** and 70% for **10c**. If the reaction was selective in the case of the methoxy-substituted substrate, giving **15c** in 44% isolated yield, the formation of **15b** in the former case was accompagnied by a reduction of the substrate leading to **18** (**15b/18** ratio = 2 from ^{1}H-NMR) and the yield of isolated **15b** was only 26%. Such a reduction reaction was already observed by us on quinolylmethyl acetates **3** (R = H) [4] although the origin of the hydride source was not yet determined. The product arising from double substitution analogous to **16** was never detected in both cases.



Scheme 8. Preparation of indole substrates **14c–d** via reduction of *N*-methylindolecarboxaldehyde. (a) $NaBH_4$ (0.6 equivalents), MeOH, 20 °C. (b) for **14c**: Ac_2O (1.1 equivalents), Et_3N, DMAP (0.1 equivalents), Et_2O, 20 °C. (c) for **14d**: *t*-BuCOCl (1.1 equivalents), Et_3N, DMAP (0.1 equivalents), Et_2O, 20 °C.



Scheme 7. Preparation of indole substrates **14a–b** via reduction of 2-indolecarboxylic acid. (a) CH_2N_2, Et_2O, 20 °C. (b) $LiAlH_4$ (one equivalent), Et_2O, 0 °C. (c) For **14a**: Ac_2O (excess), LiCl (0.1 equivalents), 20 °C. (d) For **14b**: Ac_2O (2.2 equivalents), Et_3N, DMAP (0.1 equivalents), Et_2O, 20 °C.



10a 15a 16 17

Scheme 9. Palladium-catalyzed substitution of **10a**. (a) Two equivalents of $NaCHE_2$, 2 mol% $Pd(dba)_2$, 3 mol% dppe, solvent, 60 °C. DMF, 24 h: **15a/16** = 73/27. THF, 4 h: **15a/16** = 80/20.

The reactivity of benzothiophene derivative **12** was also considerably slower than for benzofuran one **10a** since after 48 h of reaction, the conversion reached only 39% (from ^{1}H-NMR) and the selectivity in favor of the monosubstitution product was poorer since the **19/20** ratio was 84/16 (Scheme 11). Here again, the order of reactivity seems to be dictated by the relative stabilisation of the substrate since the resonance energies are in the same order for benzo derivatives as for monocyclic heterocycles [19].

The same reaction was conducted at higher (80 °C) temperature in DMF. If the reactivity (complete conversion) and the selectivity in favour of simple substitution (only 3% of double substitution product **20**), were good in these conditions, the isolated yield of **19** was only 48% because of a partial de-methoxycarbonylation reaction producing **21**. The same process occurred on **10a** when the reaction was performed in these conditions (DMF at 80 °C).

We next examined the behaviour of indole derivatives under the same reaction conditions. Substitution did not take place on **14a** and **14b** and in both cases acetate **14a** was recovered from the reaction medium, resulting probably from a deprotonation on the former and from a *N*-deacetylation of the latter. Hydrolysis during the work-up produced in both cases *N*-unprotected substrate **14a**. *N*-Methylated acetate **14c** reacted to give substitution product **22** (Scheme 12), but in low selectivity since a new side reaction appeared: after nucleophilic attack of malonate anion on carbonyl of **14c**, the produced alkoxide performed a transesterification reaction on another molecule of dimethyl malonate to produce **23**. This result indicated a very slow palladium-catalyzed process on **14c**. Like with substrates **10b** and **10c**, no product resulting from double substitution was detected. Similar results were recorded in THF at 60 °C. To suppress the competitive transesterification process, the carbonyl of the substrate was protected by a *t*-butyl group. The reaction of pivalate **14d** gave clean and selective substitution and **22** was isolated in 57% yield.

Finally the case of secondary substrates **11** and **13** was considered (Scheme 13). The steric hindrance developed by the added methyl group on the acetates disfavored an a priori double substitution reaction, so we turned back to the initial conditions (no excess of dimethyl malonate with regard to base). In fact, the only observed side reaction was as expected the elimination, producing vinylheteroaromatic compounds **26** [20] and **27** [21] as in case of quinoline and isoquinoline derivatives **3** (R = Me) and **4** [4]. The elimination products **26** and **27** resulted probably from a base-promoted hydrogen abstraction on the cationic η^3-palladium intermediate **28** (Scheme 13). Here again, the substrate **11** bearing a benzofuran aromatic system was much more reactive than its benzothiophene counterpart **13**. Moreover, the selectivity on the latter compound was poorer and elimination was the preferred pathway in THF at 60 °C. The reactivity and the selectivity were improved in DMF at higher temperature, but the isolated yield of **25** was not so good.

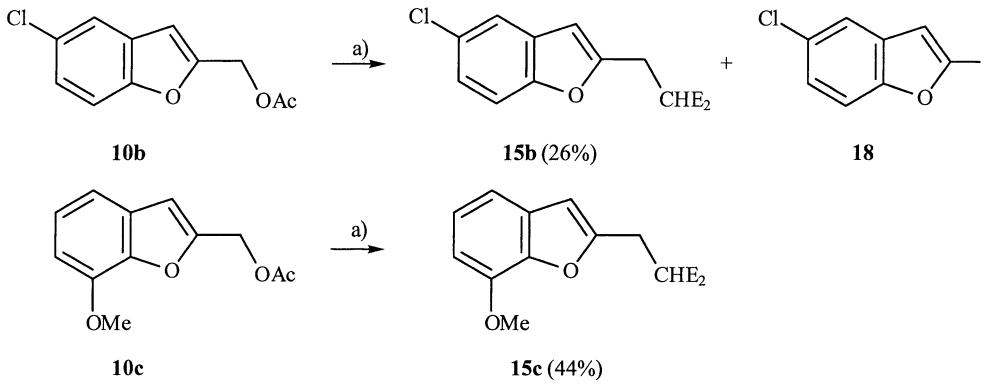
Table 1
Influence of the initial malonate/deprotonated malonate ratio on the selectivity of the palladium-catalyzed substitution reaction of **10a** [a]

n	$[CH_2E_2]/[NaCHE_2]$ [b]	**15a/16**
2	0	80/20
3	0.5	88/12
4	1	94/6 (52% isolated)
6	2	96/4

[a] **10a**, $(n-2)$ equivlalents of CH_2E_2, two equivlalents of $NaCHE_2$, 2 mol% $Pd(dba)_2$, 3 mol% dppe, THF, 60 °C, 4 h.
[b] Initial malonate/deprotonated malonate ratio.

4. Obtention of optically active substitution product 24

The asymmetric palladium-catalyzed nucleophilic substitution of racemic 1-(2-naphthyl)ethyl acetate (**1b**) was recently performed with up to 74% ee if chiral



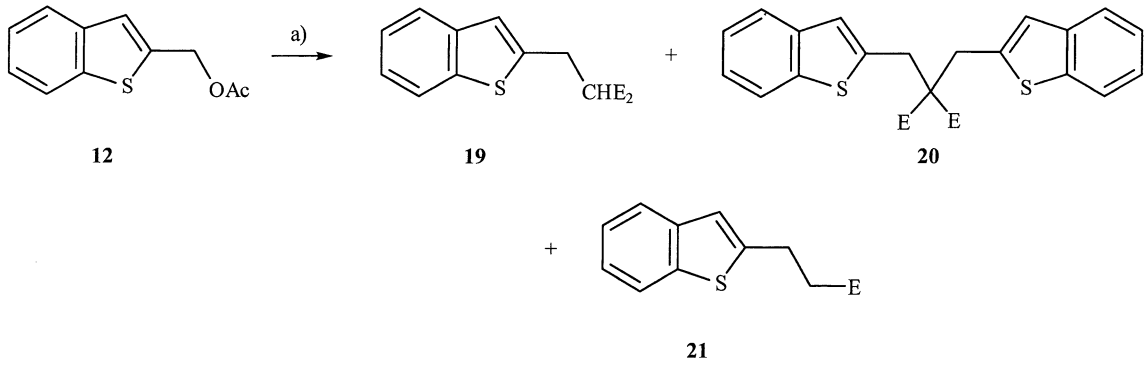
Scheme 10. Palladium-catalyzed substitution of **10b–c**. (a) Two equivalents of CH_2E_2, two equivalents of $NaCHE_2$, 2 mol% $Pd(dba)_2$, 3 mol% dppe, THF, 60 °C, 48 h.

diphosphine ligands [(*S*,*S*)-BDPP and (*R*,*R*)-Me-DUPHOS] were used [5]. In view of the poor reactivity of 1-(2-benzothienyl)ethyl acetate (**13**) compared to 1-(2-benzofuryl)ethyl acetate (**11**), we focused on the latter substrate in an asymmetric reaction but the results were disappointing (Table 2). With (*S*,*S*)-BDPP, racemic **24** was produced in very good yield (82% isolated) and with a good selectivity (**24/26** > 93/7). (*R*,*R*)-Me–DUPHOS was not the ligand of choice since it gave only a 6% yield of **24** (5% ee) beside remaining acetate **11** (53%), corresponding alcohol (29%) and some of the product of transesterification (12%) as above on indole substrate **14c**. Only (*R*)-Tol–BINAP gave a little enantioselective reaction since compound **24** was isolated with 29% ee in 16% yield (30% remaining **11** and 38% of **26**). Recovered **11** was racemic and hence no kinetic resolution process was operating to explain this result. The reaction conducted in DMF at 90 °C allowed a total conversion and a better selectivity (**24/26** = 91/9), but **24** was obtained in racemic form.

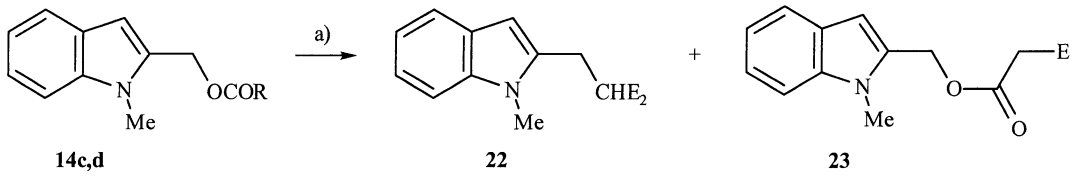
The acetate (*S*)-**11**, prepared in 67% yield from 2-iodophenol and (*S*)-but-3-yn-2-ol (Scheme 4) led to quasi-enantiopure **24** (Scheme 14). The absolute configuration of the major enantiomer was determined as (*R*) by comparison with the product of a S_N2 reaction on optically active chloride (*R*)-**29**. This latter was obtained from (*S*)-2-(hydroxyethyl)benzofuran by a recent published procedure [22] described with inversion of configuration. The ee in this reaction was very poor probably because of a low configurational stability of chloride **29**.

The palladium-catalyzed nucleophilic substitution by dimethyl malonate anion occurred stereospecifically in agreement with global retention of configuration (note that the modification of R, S descriptors was only the consequence of different sequences in **11** and in **24** according to the CIP priority rules). The stereochemistry is the same as on naphthylethyl substrates [2] and analogous to the well-known Tsuji–Trost reaction [23,24]. This result is in agreement with the inversion observed in the reported synthesis of inverto-yuehchukene [11] since organometallics and stabilized carbanions attack π-allylpalladium complexes with opposite stereochemistry (retention and inversion with respect to palladium, respectively) [24].

The poor enantioselectivity in the use of chiral palladium catalysts and the good enantiomeric excess from (*S*)-**11** with an achiral one are consistent with the following course for the transformation (Scheme 15).



Scheme 11. Palladium-catalyzed substitution of **12**. (a) 2 eq. CH_2E_2, 2 eq. $NaCHE_2$, 2 mol% $Pd(dba)_2$, 3 mol% dppe, 48 h. THF, 60 °C: **12/19/20/21** = 61/33/6/0. DMF, 80 °C: 0/70/3/27 (48% isolated).



Scheme 12. Palladium-catalyzed substitution of **14a**–**b**. (a) Two equivalents of CH_2E_2, two equivalents $NaCHE_2$, 2 mol% $Pd(dba)_2$, 3 mol% dppe, DMF, 80 °C, 48 h. **14c** (R = Me):**14c/22/23** = 51/26/25. **14d** (R = *t*-Bu): **14d/22/23** = 0/100/0 (57% isolated).

The oxidative addition on (*S*)-**11** [(*R*)-**11**] leads to intermediate (*R*)-**28** [(*S*)-**28**] (the configuration of intermediate complex **28** refers to to exocyclic asymmetric carbon atom). Both reactions have approximatly the same rate (no kinetic resolution of the substrate is observed). Nucleophilic attack of dimethyl malonate anion on (*R*)-**28** [(*S*)-**28**] produces (*R*)-**24** [(*S*)-**24**]. The two cationic intermediates (enantiomeric if L is dppe and diastereomeric if L is a chiral ligand) do not interconver (via a S_N2 process involving a Pd(0) complex [2]) at a substantial rate (compare to nucleophilic attack) and the enantiomeric ratio of the substrate is retained in the product.

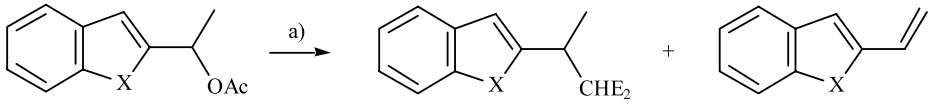
5. Conclusion

The palladium-catalyzed nucleophilic substitution was realized on some substrates containing a benzofuran, benzothiophene or indole aromatic moiety. The isolated yields of substitution products were moderate to good. Double substitution on primary acetates and elimination on secondary ones were the main observed side reactions. The stereochemistry of the substitution (overall retention of configuration) was determined. Although the asymmetric synthesis on racemic 1-(2-benzofuryl)ethyl acetate (**11**) was unsucessfull with the chiral ligands tested, the substitution product **24** was obtained with 98% ee from (*S*)-**11** using an achiral palladium catalyst when the non-catalyzed S_N2 reaction of chloride **29** showed considerable racemization. Unlike the same reaction on naphthalene derivatives [2], the interconversion of cationic intermediate complexes is very slow compared to nucleophilic attack.

6. Experimental

6.1. General

^1H- and ^{13}C-NMR spectra were recorded on a Bruker AC-250 MHz spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Coupling constants are

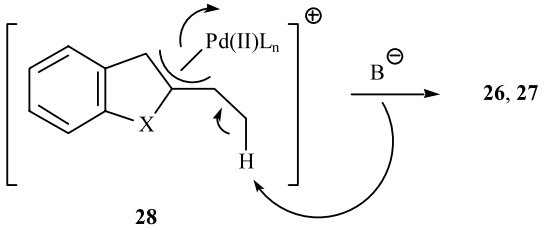


11 X = O
13 X = S

24 X = O
25 X = S

26 X = O
27 X = S

Substrate	Conditions	Remaining Acetate (%)	Substitution (%)	Elimination (%)
11	THF, 60°C	0	84 (71% isolated)	16
13	THF, 60°C	17	29	54
13	DMF, 80°C	0	84 (48% isolated)	16



Scheme 13. Palladium-catalyzed substitution of **11** and **13**. (a) Two equivalents of $NaCHE_2$, 2 mol% $Pd(dba)_2$, 3 mol% dppe, 48 h.

Table 2
Asymmetric palladium-catalyzed substitution of racemic **11** [a]

Chiral ligand	Conditions	Recovered **11** (%)	**24** (% ee)	**26**
(*S*,*S*)-BDPP [b]	THF, 60 °C	0	82 (0)	< 7
(*R*,*R*)-Me–DUPHOS [c]	THF, 60 °C	53	6 (5)	0
(*R*)-Tol–BINAP [d]	THF, 60 °C	30	16 (29)	38
(*R*)-Tol–BINAP	DMF, 90 °C	0	79 (0)	9

[a] **11**, two equivlalents of $NaCHE_2$, 2 mol% $Pd(dba)_2$, 2.5 mol% chiral ligand, 48 h.
[b] (*S*,*S*)-BDPP = (2*S*,4*S*)-2,4-bis(diphenylphosphino)pentane.
[c] (*R*,*R*)-Me–DUPHOS = 1,2-bis((2*R*,5*R*)-2,5-dimethylphospholano)benzene.
[d] (*R*)-Tol–BINAP = (*R*)-2,2′-bis(di-p-tolylphosphino)-1,1′-binaphthyl.

reported in Hz. Optical rotations were measured at 20 °C on a Perkin Elmer 241 polarimeter.

All reactions involving palladium catalysis were carried out under argon using Schlenk techniques under an argon atmosphere. Tetrahydrofuran (THF) was distilled under argon from sodium/benzophenone under nitrogen. Dimethylformamide (DMF) was dried over CaH_2 and distilled prior to use.

$Pd(dba)_2$ (dba denotes dibenzylideneacetone) [25] and 2-benzothiophenecarboxaldehyde [26] were prepared according to reported procedures.

Byproducts **18**, **20**, **21** and **23** could not be isolated in pure form and were identified by mass spectrometry.

6.2. 2-Benzofurylmethyl acetate (*10a*)

2-Iodophenol (4.4 g, 20 mmol), $PdCl_2(PPh_3)_2$ (430 mg, 0.6 mmol, 3 mol%), CuI (150 mg, 0.8 mmol, 4 mol%), and Et_3N (6 ml, 40 mmol) were dissolved in 10 ml of DMF. After 15 min stirring, propargyl alcohol (1.2 ml, 20 mmol) was added dropwise over 5 min. The reaction mixture was stirred 1 h at room temperature (r.t.), then overnight at 60 °C, cooled and poured into 50 ml of water. The aqueous phase was extracted by 3 × 30 ml of dichloromethane. The combined organic phases were washed successively by 3 × 50 ml of 5 M NaOH and 3 × 100 ml of water, dried over $MgSO_4$ and concentrated.

The residual dark-brown oil was dissolved in Ac_2O (3.8 ml, 40 mmol) and LiCl (78 mg, 1.8 mmol) was added. After stirring overnignt at r.t., the reaction mixture was diluted with 20 ml of ether, washed twice by 10 ml of a saturated Na_2CO_3 solution. The aqueous phases were extracted by 3 × 15 ml of ether and the combined ethereal phases were dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (silica, heptane/ethyl acetate 80:20). After Kügelrohr distillation (115 °C, 0.1 mmHg), **10a** [27] was obtained as a colorless oil (2.66 g, 14 mmol, 70%).

^{1}H-NMR 2.10 (3H, s), 5.19 (2H, s), 6.75 (1H, s), 7.18–7.21 (1H, m), 7.29 (1H, dd, $J = 7.5$ and 1.3), 7.47 (1H, d, $J = 8$), 7.55 (1H, dd, $J = 8.3$ and 1.2). ^{13}C-NMR 20.6, 58.3, 106.8, 112.0, 121.2, 122.8, 124.7, 127.7, 151.7, 155.0, 170.3.

6.3. 2-(5-Chloro)benzofurylmethyl acetate (*10b*)

2-Bromo-4-chlorophenol (415 mg, 2 mmol), $PdCl_2(PPh_3)_2$ (140 mg, 0.2 mmol, 10 mol%), CuI (18 mg, 0.09 mmol, 5 mol%), and Et_3N (0.6 ml, 4 mmol) were dissolved in 5 ml of DMF. After 15 min stirring, propargyl alcohol (0.2 ml, 3.3 mmol) was added dropwise over 5 min. The reaction mixture was stirred one hour at r.t., then overnight at 100 °C. The treatment, acetylation of the crude alcohol, and purification were conducted as above for **10a,** and compound **10b** was obtained as an oil (155 mg, 0.7 mmol, 34%).

^{1}H-NMR 2.10 (3H, s), 5.16 (2H, s), 6.69 (1H, s), 7.23 (1H, dd, $J = 8.8$ and 1.9), 7.37 (1H, d, $J = 8.8$), 7.50 (1H, d, $J = 1.9$). ^{13}C-NMR 20.7, 58.3, 106.4, 112.3, 120.8, 125.0, 128.5, 129.2, 131.9, 153.4, 170.4. HRMS Calc. for $C_{11}H_9ClO_3$: 224.02406. Found: 224.0240.

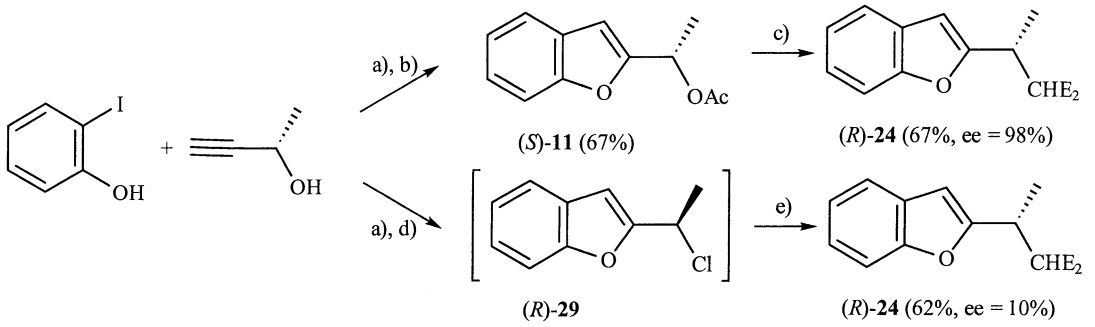
6.4. 2-(7-Methoxy)benzofurylmethyl acetate (*10c*)

7-Methoxy-2-benzofurancarboxylic acid (480 mg, 2.5 mmol) was dissolved in 5 ml of THF under argon. At 0 °C, BH_3.THF complex (2.5 ml, 2.5 mmol) was added dropwise. After 6 h stirring at r.t., the solution was cooled at 0 °C and 20 ml of HCl 1M were added. The aqueous phase was extracted by 3 × 20 ml of ether and the organic phases were washed by 20 ml of a $NaHCO_3$ saturated solution, dried (K_2CO_3) and concentrated. The crude alcohol was dissolved in Ac_2O (1 ml, 10 mmol), in the presence of LiCl (10 mg, 0.25 mmol). After stirring overnight and dilution with 20 ml of ether, the reaction mixture was washed twice with 10 ml of a saturated $CaCO_3$ solution, and the aqueous phases were extracted by 3 × 15 ml of ether. The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (silica, heptane/ethyl acetate 80:20). Compound **10c** (313 mg, 1.4 mmol, 57%) was obtained as an oil.

^{1}H-NMR 2.08 (3H, s), 3.99 (3H, s), 5.18 (2H, s), 6.75 (1H, s), 6.80 (1H, t, $J = 4.4$), 7.14 (2H, d, $J = 4.4$). ^{13}C-NMR 10.7, 55.8, 58.3, 106.6, 107.2, 113.4, 123.5, 129.4, 144.4, 145.2, 151.9, 170.3. HRMS Calc. for $C_{12}H_{12}O_4$: 220.0736. Found: 220.0728.

6.5. 1-(2-Benzofuryl)ethyl acetate *11*

Following the same procedure as above for **10a**, substituting propargyl alcohol by but-3-yn-2-ol (1.6



Scheme 14. Determination of the stereochemistry of the palladium-catalyzed substitution of (*S*)-**11**. (a) 3 mol% $Pd(PPh_3)_2Cl_2$, 4 mol% CuI, Et_3N, DMF, 60 °C. (b) Ac_2O (excess), LiCl (0.1 equivalents), 20 °C. (c) Two equivalents of $NaCHE_2$, 2 mol% $Pd(dba)_2$, 3 mol% dppe, DMF, 80 °C, 48 h. (d) 2,4,6-trichloro-1,3,5-triazine, DMF, CH_2Cl_2, 20 °C, 12 h. (e) Two equivalents $KCHE_2$, DMF, 20 °C, 72 h.

ml, 20 mmol), compound **11** [28] (2.36 g, 11.6 mmol, 58%) was obtained as a colorless oil. The two enantiomers were resolved by HPLC analysis with chiral stationary-phase column WHELK 01 [hexane/isopropanol 98/2, 1 ml min^{-1}, $t = 6.6$ min, 10.1 min].

^{1}H-NMR 1.65 (3H, d, $J = 6.8$), 2.08 (3H, s), 6.07 (1H, q, $J = 6.8$), 6.67 (1H, s), 7.13–7.34 (2H, m), 7.43–7.48 (1H, m), 7.50–7.55 (1H, m). ^{13}C-NMR 18.0, 20.6, 65.1, 103.9, 111.0, 120.9, 122.6, 124.2, 127.6, 154.5, 155.7, 170.0.

(*S*)-**11** ($[\alpha]_D^{20} = -167$ (*c* 1.2, MeOH)) was obtained in 67% yield from 2-iodophenol and (*S*)-but-3-yn-2-ol.

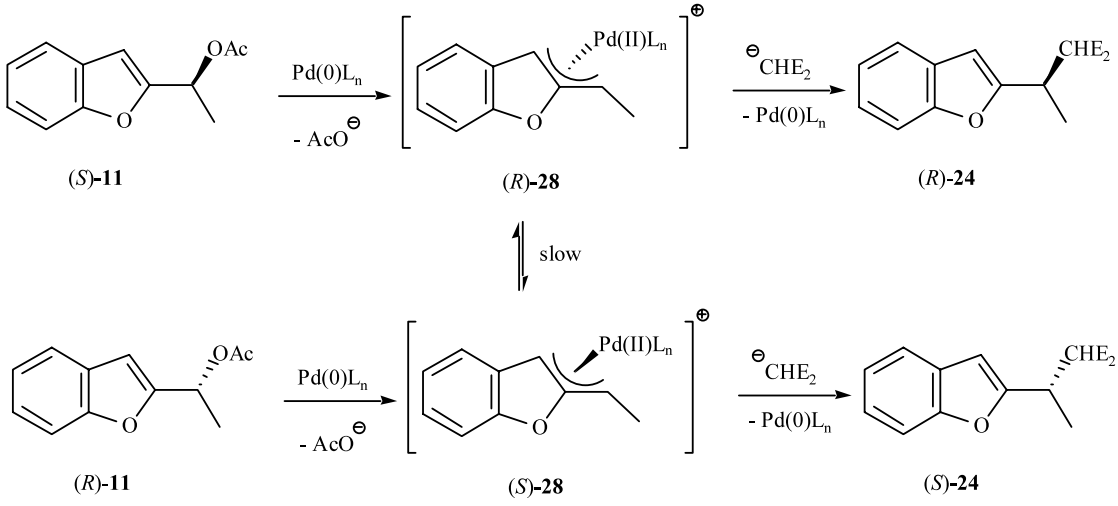
6.6. 2-Benzothiophenylmethyl acetate (*12*)

2-Benzothiophenecarboxaldehyde (225 mg, 1.4 mmol) was dissolved in 5 ml of methanol. $NaBH_4$ (27 mg, 0.7 mmol) was added portionwise. After TLC control, 10 ml of 1 M HCl were added and the reaction mixture was extracted by 3×20 ml of ether. The combined organic phases were dried ($MgSO_4$) and concentrated to give 212 mg of a white solid. The alcohol was stirred overnight in Ac_2O (1 ml, 10 mmol) in the presence of LiCl (10 mg, 0.25 mmol). After dilution (20 ml of ether) and washing (3×10 ml of a saturated Na_2CO_3 solution), the aqueous phases were extracted (3×20 ml of ether). The combined ethereal phases were dried ($MgSO_4$) and concentrated to give **12** (229 mg, 1.1 mmol, 79%) as a white solid, m.p. 78–79 °C (lit.: 79–80 °C) [29].

^{1}H-NMR 2.10 (3H, s), 5.33 (2H, s), 7.28–7.33 (3H, m), 7.71–7.82 (2H, m). ^{13}C-NMR 20.7, 61.1, 122.2, 123.6, 124.21, 124.24, 124.5, 138.6, 139.0, 140.2, 170.4.

6.7. 1-(2-Benzothiophenyl)ethyl acetate (*13*)

2-Benzothiophenecarboxaldehyde (486 mg, 3 mmol) was dissolved in 10 ml of anhydrous ether. Methylmagnesium bromide (1.1 ml of a 3 M solution in ether, 3.3 mmol) was added dropwise at 0 °C to give a heterogeneous mixture. After TLC control, 20 ml of a cold 1 M HCl solution were added and the reaction mixture was extracted by 3×20 ml of ether. The combined



Scheme 15. Stereochemical course of the palladium-catalyzed substitution of **11**.

organic phases were neutralized (20 ml of a saturated $NaHCO_3$ solution), washed by 2×20 ml of water, dried ($MgSO_4$), and concentrated. The crude alcohol was stirred overnight in Ac_2O (1 ml, 10 mmol) in the presence of LiCl (13 mg, 0.3 mmol). After dilution (20 ml of ether) and washing (3×10 ml of a saturated Na_2CO_3 solution), the aqueous phases were extracted (3×20 ml of ether). The combined ethereal phases were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (silica, heptane/ethyl acetate 90:10) to give **13** [28] (541 mg, 2.46 mmol, 82%) as an oil.

^{1}H-NMR 1.67 (3H, d, $J = 6.4$), 2.07 (3H, s), 6.20 (1H, q, $J = 6.3$), 7.23 (1H, s) 7.27–7.35 (2H, m), 7.68–7.72 (1H, m), 7.76–7.79 (1H, m). ^{13}C-NMR 21.2, 21.9, 68.1, 121.6, 122.3, 123.7, 124.3, 124.4, 139.3, 145.0, 170.1.

6.8. 2-Indolylmethyl acetate (*14a*)

2-Indolylmethanol [16] (2.27 g, 15.5 mmol) was dissolved in Ac_2O (3 ml, 31 mmol) and LiCl (67 mg, 1.5 mmol) was added. After stirring overnignt at r.t., the reaction mixture was diluted with 20 ml of ether, washed twice by 10 ml of a saturated Na_2CO_3 solution. The aqueous phases were extracted by 3×15 ml of ether and the combined ethereal phases were dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (silica, heptane/ethyl acetate 80:20) and **14a** was obtained as a yellow oil (315 mg, 1.7 mmol, 11%).

^{1}H-NMR 2.09 (3H, s), 5.21 (2H, s), 6.53 (1H, s), 7.08 (1H, t, $J = 7.4$), 7.20 (1H, t, $J = 7.5$), 7.34 (1H, d, $J = 7.9$) 7.58 (1H, d, $J = 7.7$), 8.58 (1H, s). ^{13}C-NMR 21.4, 60.1, 104.3, 111.5, 120.3, 121.3, 123.2, 127.9, 133.4, 136.9, 172.7.

6.9. 2-(N-Acetyl)indolylmethyl acetate (*14b*)

2-Indolylmethanol [16] (1.56 g, 10.6 mmol) was dissolved in Et_2O (15 ml). Triethylamine (2.2 ml, 13 mmol), DMAP (130 mg, 1 mmol) and dropwise Ac_2O (2.2 ml, 23 mmol) were added. After stirring overnignt at r.t., the reaction mixture was hydrolyzed by 10 ml of a saturated Na_2CO_3 solution. The organic phase was washed twice by 10 ml of a saturated Na_2CO_3 solution, dride over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (silica, heptane/ethyl acetate 80:20) and **14b** was obtained as a white solid (2.03 g, 8.8 mmol, 83%).

^{1}H-NMR 2.14 (3H, s), 2.79 (3H, s), 5.48 (2H, s), 6.68 (1H, s), 7.21–7.34 (2H, m), 7.54 (1H, t, $J = 7.3$), 7.79 (1H, d, $J = 8.2$). ^{13}C-NMR 20.9, 26.9, 61.0, 110.7, 114.5, 120.7, 121.2, 122.6, 123.2, 124.5, 129.4, 136.0, 170.3.

6.10. 2-(N-Methyl)indolylmethyl acetate (*14c*)

N-Methylindolecarboxaldehyde (795 mg, 5 mmol) was dissolved in 20 ml of methanol. $NaBH_4$ (114 mg, 3 mmol) was added portionwise. After TLC control, 10 ml of 1M HCl were added, then the reaction mixture was neutralized by NaOH. The reaction mixture was extracted by 3×20 ml of ether. The combined organic phases were dried ($MgSO_4$) and concentrated. The crude alcohol was disolved in 10 ml of ether, Et_3N (1 ml, 6 mmol), DMAP (60 mg, 0.5 mmol), then dropwise Ac_2O (0.5 ml, 5.5 mmol) were added. The resulting mixture was stirred overnight and hydrolyzed by a saturated Na_2CO_3 solution. The organic phase was washed twice by saturated Na_2CO_3, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (silica, heptane/ethyl acetate 80:20) to give **14c** (700 mg, 3.44 mmol, 69%) as a yellow solid, m.p. 73–75 °C.

^{1}H-NMR 2.08 (3H, s), 3.76 (3H, s), 5.26 (2H, s), 6.57 (1H, s), 7.08–7.12 (1H, m), 7.20–7.33 (2H, m), 7.58 (1H, d, $J = 7.8$). ^{13}C-NMR 20.8, 29.6, 58.0, 103.7, 109.2, 119.6, 120.9, 122.2, 127.0, 133.5, 137.9, 170.4. HRMS Calc. for $C_{12}H_{13}NO_2$: 203.0946. Found: 203.0935.

6.11. 2-(N-Methyl)indolylmethyl pivalate (*14d*)

The same procedure as above for **14c**, substituting acetic anhydride by pivaloyl chloride, gave compound **14d** (87%) as a yellow oil.

^{1}H-NMR 1.20 (9H, s), 3.73 (3H, s), 5.25 (2H, s), 6.56 (1H, s), 7.08-7.11 (1H, m), 7.23–7.31 (2H, m), 7.59 (1H, d, $J = 7.8$). ^{13}C-NMR 26.3, 26.9, 29.5, 58.2, 103.3, 109.0, 119.4, 120.7, 121.9, 126.9, 133.8, 137.8, 177.7. HRMS Calc. for $C_{15}H_{19}NO_2$: 245.1416. Found: 245.1420.

6.12. General nucleophilic palladium-catalyzed procedure

2-Benzofurylmethyl acetate (**10a**) (190 mg, 1 mmol) in 1 ml of THF was added under argon to a solution of $Pd(dba)_2$ (11.5 mg, 0.02 mmol, 2 mol%) and dppe (12 mg, 0.03 mmol, 3 mol%) in 1 ml of THF. Dimethyl malonate (0.46 ml, 4 mmol) was added dropwise on a suspension of sodium hydride (48 mg, 2 mmol) in 3 ml of THF. The resulting mixture was heated to 60 °C during 15 min, when added by canula to the substrate–catalyst solution. The reaction mixture was stirred at 60 °C for 24 h, then diluted with ether (20 ml) and the organic phase washed with 2×15 ml of a solution of saturated $NaHCO_3$. The aqueous phases were extracted with ether (3×20 ml) and the combined ethereal phases were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (silica, heptane/ethyl acetate 80:20) to give dimethyl 2-(2-benzofurylmethyl)propanedioate **15a** (136 mg, 0.52 mmol, 52%).

*6.12.1. Dimethyl 2-(2-benzofurylmethyl)propanedioate (**15a**) (52% isolated yield)*

^{1}H-NMR 3.73 (6H, s), 3.62–3.88 (3H, m), 6.45 (1H, s), 7.16–7.23 (2H, m), 7.35–7.40 (1H, m), 7.45–7.49 (1H, m). ^{13}C-NMR 27.7, 50.1, 52.6, 103.7, 110.7, 120.5, 122.5, 123.6, 128.3, 154.4, 154.6, 168.6. HRMS Calc. for $C_{14}H_{14}O_5$: 262.0841. Found: 262.0835.

*6.12.2. Dimethyl 2,2-di(2-benzofurylmethyl)propanedioate (**16**) (41% isolated yield from the reaction of (**10a**) with two equivalents of sodium salt of **15a**)*

^{1}H-NMR 3.44 (4H, s) 3.81 (6H, s), 6.57 (2H, s), 7.19–7.23 (4H, m), 7.35–7.42 (2H, m), 7.45–7.56 (2H, m). ^{13}C-NMR 31.4, 52.7, 57.0, 105.9, 110.8, 120.4, 122.6, 123.8, 128.2, 153.3, 154.8, 170.1. HRMS Calc. for $C_{23}H_{20}O_6$: 392.1260. Found: 392.1266.

*6.12.3. Dimethyl 2-(2-(5-chloro)benzofurylmethyl)propanedioate (**15b**) (26% isolated yield)*

^{1}H-NMR 3.72 (6H, s), 3.63-3.90 (3H, m), 6.40 (1H, s), 7.09–7.31 (2H, m), 7.42 (1H, d, $J = 2$). ^{13}C-NMR 27.8, 50.1, 52.8, 103.5, 111.8, 120.2, 123.9, 127.5, 128.1, 128.5, 156.1, 168.6. HRMS Calc. for $C_{14}H_{13}ClO_5$: 296.0452. Found: 296.0444.

*6.12.4. Dimethyl 2-(2-(7-methoxy)benzofurylmethyl)propanedioate (**15c**) (44% isolated yield)*

^{1}H-NMR 3.40 (2H, d, $J = 7.6$), 3.72 (6H, s), 3.88 (1H, t, $J = 7.6$), 3.97 (3H, s), 6.45 (1H, s), 6.73 (1H, dd, $J =$ 6.4 and 2.4), 7.06–7.10 (2H, m). ^{13}C-NMR 27.8, 50.3, 52.8, 56.0, 104.3, 106.0, 113.0, 123.3, 128.2, 128.5, 136.0, 154.6, 168.7. HRMS Calc. for $C_{15}H_{16}O_6$: 292.0947. Found: 292.0943.

*6.12.5. Dimethyl 2-(2-benzothiophenylmethyl)propanedioate (**19**) (48% isolated yield in DMF at 80 °C)*

^{1}H-NMR 3.51 (2H, d, $J = 7.6$), 3.72 (6H, s), 3.79 (1H, t, $J = 7.6$), 7.05 (1H, s), 7.22–7.32 (2H, m), 7.63–7.67 (1H, m), 7.72–7.75 (1H, m). ^{13}C-NMR 29.8, 52.7, 53.2, 122.1, 122.6, 123.1, 123.9, 124.2, 139.5, 139.7, 140.7, 168.6. HRMS Calc. for $C_{14}H_{14}O_4S$: 278.0613. Found: 278.0603.

*6.12.6. Dimethyl 2-(2-(N-methyl)indolylmethyl)propanedioate (**22**) (57% isolated yield in DMF at 80 °C)*

^{1}H-NMR 3.39 (2H, d, $J = 7.6$), 3.69 (6H, s), 3.74 (3H, s), 3.86 (1H, t, $J = 7.6$), 6.27 (1H, s), 7.05–7.09 (1H, m), 7.13–7.20 (1H, m), 7.23–7.28 (1H, m), 7.51 (1H, d, $J =$ 7.7). ^{13}C-NMR 25.9, 29.4, 51.0, 52.8, 99.4, 108.8, 119.3, 120.0, 121.0, 127.5, 136.5, 137.3, 168.9. HRMS Calc. for $C_{15}H_{17}NO_4$: 275.1158. Found: 275.1147.

*6.12.7. Dimethyl 2-(1-(2-benzofuryl)ethyl)propanedioate (**24**) (82% isolated yield using two equivalents of dimethyl malonate with (S,S)-BDPP as palladium ligand)*

^{1}H-NMR 1.41 (3H, d, $J = 6.3$), 3.60 (3H, s), 3.74 (3H, s), 3.66–3.85 (2H, m), 6.45 (1H, s), 7.12–7.21 (2H, m), 7.37–7.40 (1H, m), 7.45–7.48 (1H, m). ^{13}C-NMR 16.5, 33.7, 52.4, 56.0, 102.4, 110.7, 120.5, 122.4, 123.5, 128.2, 154.4, 158.8, 168.0. HRMS Calc. for $C_{15}H_{16}O_5$: 276.0998. Found: 276.0997. The two enantiomers were resolved by HPLC analysis with chiral stationary-phase column WHELK 01 [hexane/isopropanol 98/2, 1 ml min^{-1}, $t = 12.6$ min, 16.5 min].

(*R*)-**24**: $[\alpha]_D^{20} = -34$ (c 1.7, MeOH) for a sample with 98% ee.

*6.12.8. Dimethyl 2-(1-(2-benzothiophenyl)ethyl)propanedioate (**25**) (48% isolated yield using two equivalents of dimethylmalonate in DMF at 80 °C)*

^{1}H-NMR 1.44 (3H, d, $J = 6.8$), 3.56 (3H, s), 3.76 (3H, s), 3.63–3.97 (2H, m), 7.08 (1H, s), 7.15–7.19 (1H, m), 7.25–7.30 (1H, m), 7.64–7.68 (1H, m), 7.72–7.77 (1H, m). ^{13}C-NMR 20.3, 36.0, 52.4, 52.5, 59.1, 121.0, 122.1, 123.1, 123.8, 124.1, 138.9, 139.4, 147.2, 167.9, 168.1. HRMS Calc. for $C_{15}H_{16}O_4S$: 292.0769. Found: 292.0764.

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