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Acyclic ene-carbamate. A useful tool for an original synthesis of phosphine-containing α-amino acids bearing a quaternary carbon

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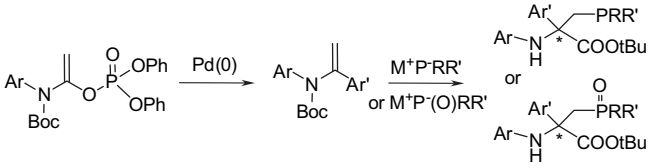
ABSTRACT

A novel and efficient approach for the synthesis of phosphine-containing α-amino acids bearing quaternary carbon is described. The key step involves the original nucleophilic addition of lithiated phosphines onto acyclic ene-carbamates concomitant with a spontaneous internal (N→C) alkyloxycarbonyl migration.

1. Introduction

The development of new synthetic approaches to non-natural amino acids is a blossoming field of research since such compounds have found applications in the synthesis of pharmacologically useful molecules, analogues of bioactive peptides mimetics. Phosphine-containing amino acids are of interest with respect to their biological properties[1] but are also useful building blocks for the synthesis of amino-functional phosphines, *P,N*-heterocycles or hybrid ligands.[2] As a consequence, developing new routes to highly functionalized phosphine containing amino acids remains a great challenge. Most phosphines are synthesized by addition of a Grignard or organolithium reagent to a phosphine chloride, by reaction of phosphide anions with an electrophile[3] or by metal-catalyzed reaction.[4,2e] In order to facilitate the synthesis of a phosphine-containing amino acid core, we focused on a new approach that uses the nucleophilic addition of lithiated phosphine onto the double bond of acyclic ene-carbamates (cf. Scheme 1). Examples of nucleophilic addition reactions of phosphane derivatives to a variety of functionalized alkenes have been reported in the literature.[2c,2d,2g] We have recently described an original and efficient synthesis of precursors of α-amino acids that was performed via an intermolecular carbolithiation reaction onto acyclic ene-carbamates. This key step was concomitant with a spontaneous internal (N→C) alkyloxycarbonyl migration which led to quaternary aminoesters.[5] Accordingly, we wondered if we could extend the scope of this reaction and so devise a new route to phosphine-containing α-amino-acids (Scheme 1). The strategy involved was expected to offer the potential advantage of directly introducing further molecular diversity onto the molecules as a result of the original choice of the starting primary amine, the phospholithium reagent or the palladium coupling agent. The first part of this work will concern the preparation of acyclic ene-carbamates from the corresponding vinylphosphates via a palladium cross-coupling reaction. The nucleophilic addition of lithiated phosphines onto the latter will be investigated in a second stage. The method is significant in that it represents a potential general route to enantiomerically pure phosphine- and/or phosphane oxides- containing α-amino acids.



Scheme 1. General route envisioned to phosphine- or phosphane oxides- containing α-amino-acids.

2. Results and discussion

Our previous results[5] allowed us to realize the synthesis of the original acyclic amide-derived vinylphosphates **3**. Starting from aromatic primary amines **1**, after protection of the nitrogen, the amide **2** was treated with LDA (1.2 equiv) at −78 °C in THF providing the desired lithium enolate, that was quenched with diphenylchlorophosphate (1.2 equiv) (cf. Table 1). After workup and purification by silica gel chromatography, the required acyclic amide-derived vinylphosphates **3a–c** were isolated in good yields. A Pd-catalyzed Suzuki–Miyaura coupling or Stille cross-coupling reaction was then investigated. By using classical conditions and as previously demonstrated, a range of acyclic ene-carbamates **4a–k**, substituted alpha to nitrogen by different aryl or heteroaryl groups, was isolated in fair to good yields (cf. Table 2).

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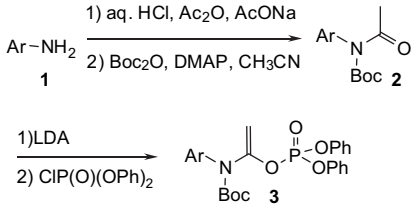
Table 1
Preparation of acyclic amide-derived vinylphosphates **3a–c**



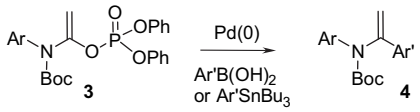
Entry	Ar	Amide **2**[a] (yield %)	Vinylphosphate **3**[c] (yield %)
1	Ph	**2a**[a] (82%)	**3a** 83%
2	2-MeC$_6$H$_4$	**2b**[a] (61%)	**3b** 82%
3	Bn	**2c**[b] (82%)	**3c** 90%

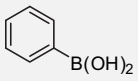
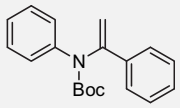
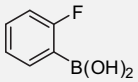
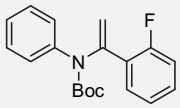
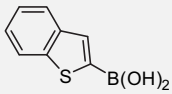
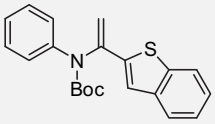
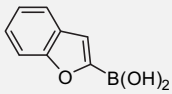
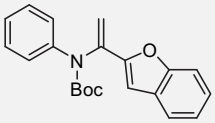
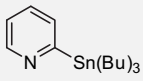
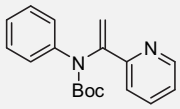
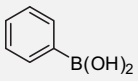
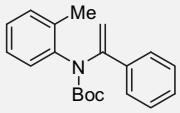
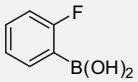
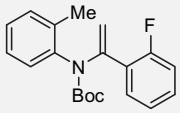
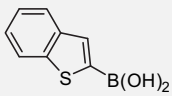
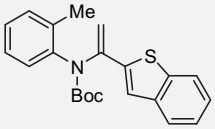
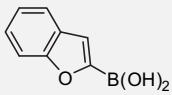
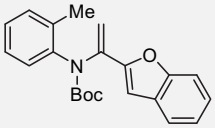
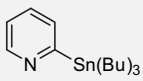
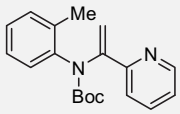
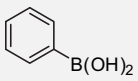
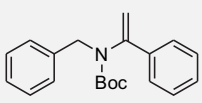
[a] Conditions: (i) aqueous HCl, Ac_2O, AcONa, rt, 15 min. (ii) Boc_2O, DMAP, CH_3CN, rt, 15 h.
[b] The acetamide was synthetized from benzylamine by refluxing 30 min in acetic anhydride.
[c] (i) 1.2 equiv LDA, THF, −78 °C, 1h30. (ii) 1.2 equiv ClP(O)(OPh)$_2$, −78 °C, 2 h.

Access to phosphine-containing amino acids was then considered, and acyclic ene-carbamates **4a–k** were submitted to Ph_2PLi (cf. Table 3). Treatment of **4a**, chosen as a model, with three equivalents of Ph_2PLi in THF at −78 °C, followed by warming of the reaction mixture to room temperature, led to the desired derivative **5a** (see entry 1, Table 3). As previously demonstrated, a spontaneous internal (N→C) alkyloxycarbonyl migration occurred, which, after hydrolysis, provided α-aminoesters **5a–j**, direct precursors of α-amino acids bearing a quaternary carbon next to the nitrogen. Theoretical studies reported by Hook and Bailey[6] reveal that the initial step for the intermolecular carbometalation is an energetically favorable coordination of the lithium atom with the π-system. The π-chelation was also promoted by a Complex Induced Proximity Effect (CIPE)[7] of the carbamate donor. By warming the reaction mixture to room temperature, the benzylic organolithium type intermediate became thermally labile and spontaneously underwent an internal Boc carbonyl migration from the nitrogen to the benzylic carbon via a strained three-membered ring[8] to give α-aminoesters **5** (Fig. 1).

It is worth noting that a spontaneous over-oxidation of phosphine-based derivatives could be observed during the hydrolysis process, during the purification step on column chromatography or while left standing in the air. However, the conversion of phosphine oxides to phosphines could be performed with silanes or hydride reducing agents. Structures **5e**, **5f** and **5k** were unambiguously determined by X-ray analyses (see Supplementary data).[9] In the case of benzodioxinic derivatives **4d** or **4i**, only decomposition products were observed. For compounds **5b** or **5g**, no further fluoride substitution occurred. Additionally to the unavoidable over-oxidation, and according to the quantity of lithiated phosphine present in the reaction, a mixture of transferred or untransferred compounds could also be observed in some cases. In the aim of rationalizing these results, we decided to study the ratio of free and lithiated phosphine, considering a possible effect on the path of the reaction (Table 4). In the case of compound **4a** (R_1, R_2=Ph), it clearly appeared that the presence of non lithiated phosphine improves the formation of the untransferred products (see entries 1,2 and 3, Table 4). For pyridinyl derivative **4e** (R_1=Ph, R_2=Py) (entries 4 and 5, Table 4), the presence of only one equivalent of free phosphine led to the complete formation of untransferred product, allowing us to say that the in situ reprotonation is considerably faster than the intramolecular transfer of the Boc group. Finally, benzylic compound **4k** (R_1=Bn, R_2=Ph) (entry 6, Table 4), even in the absence of free phosphine, led to the complete formation of the oxidized untransferred compound owing to the slow rate of the nucleophilic addition of lithium phosphide onto the double bond of the ene-carbamate.

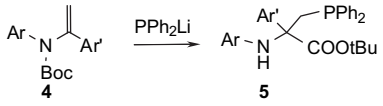
Table 2
Preparation of acyclic ene-carbamates **4a–k** via Suzuki–Miyaura or Stille cross-coupling reaction

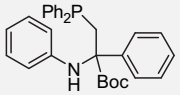
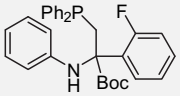
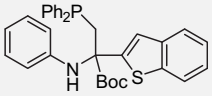
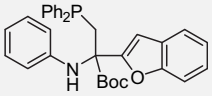
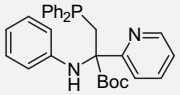
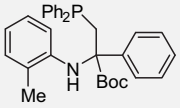
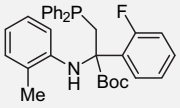
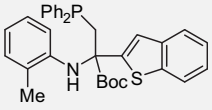
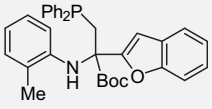
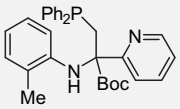
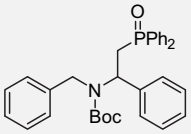


Entry	Ar	Ar′B(OH)$_2$ Or Ar′SnBu$_3$	Products	Yield (%)
1[a]	Ph			**4a**[5] 83%
2[a]	Ph			**4b** 46%
3[a]	Ph			**4c** 88%
4[a]	Ph			**4d** 74%
5[b]	Ph			**4e** 81%
6[a]	2-MeC$_6$H$_4$			**4f** 90%
7[a]	2-MeC$_6$H$_4$			**4g** 64%
8[a]	2-MeC$_6$H$_4$			**4h** 89%
9[a]	2-MeC$_6$H$_4$			**4i** 94%
10[b]	2-MeC$_6$H$_4$			**4j** 78%
11[a]	Bn			**4k** 81%

[a] Conditions: 2.5 equiv. ArB(OH)$_2$, 10 mol % $PdCl_2(PPh_3)_2$, 2 equiv aqueous Na_2CO_3 2 M, a few drops of EtOH, THF, reflux 30 min-1 h.
[b] 2.5 equiv. RSnBu$_3$, 10 mol % $PdCl_2(PPh_3)_2$, 2 equiv. LiCl, toluene, 18 h, reflux.

Table 3
Nucleophilic addition of Ph_2PLi onto acyclic ene-carbamates **4a–k**[a]



Entry	Ar	Ene-carbamates	Products	Yield (%)
1	Ph	**4a**		**5a** 43%
2	Ph	**4b**		**5b** 41%
3	Ph	**4c**		**5c** 95%
4	Ph	**4d**		**5d** 0%
5	Ph	**4e**		**5e** 47%
6	2-MeC$_6$H$_4$	**4f**		**5f** 43%
7	2-MeC$_6$H$_4$	**4g**		**5g** 55%
8	2-MeC$_6$H$_4$	**4h**		**5h** 54%
9	2-MeC$_6$H$_4$	**4i**		**5i** 0%
10	2-MeC$_6$H$_4$	**4j**		**5j** 0%
11	Bn	**4k**		**5k** 50%

[a] Conditions: 3 equiv. Ph_2PLi, THF, −78 °C to rt, 15 min.

However, considering the favorable conditions of the Boc transfer process (see Table 3), attempts to trap, via an intermolecular way, the potential intermediate lithium anion by various electrophiles were made but remained unsuccessful. Also, in order to get enantiopure precursors of α-amino-acids, the synthesized phosphide anion was first complexed with (−)-sparteine in order to induce stereoselectivity during the nucleophilic attack onto the double bond of the ene-carbamate. Nevertheless, it appeared that no stereoselectivity was induced on the substrate even by conducting the reaction at low temperature.[10] This unfortunate result may be due to a racemization process which occurred during the spontaneous Boc transfer.

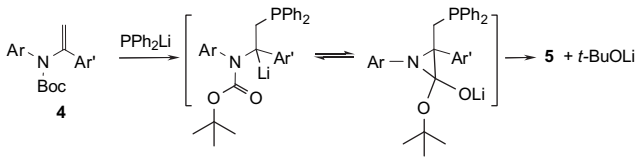
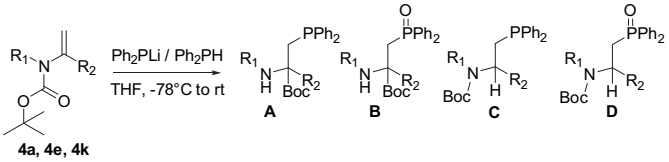


Figure 1. Mechanistic proposal for the intramolecular (N→C) Boc migration.

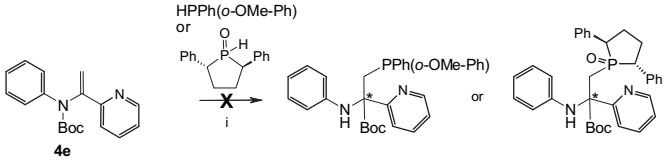
Table 4
Influence of the ratio Ph_2PH/Ph_2PLi on the nucleophilic addition onto acyclic ene-carbamates **4a**, **4e** and **4k**[a]



Entry	Ratio Ph_2PH/Ph_2PLi	SM[b]	R_1	R_2	Products Ratio A/B/C/D (%)							
					A		B	C			D	
1	0/3	**4a**	Ph	Ph	**5a**	100	0	0			0	
2	2/2	**4a**	Ph	Ph	**5a**	39	0	**6a**	35	**6b**	24	
3	2/1	**4a**	Ph	Ph	**5a**	30	0	**6a**	62	**6b**	9	
4	0/3	**4e**	Ph	Py	**5e**	100	0	0			0	
5	1/2	**4e**	Ph	Py		0	0	0		**6c**	100	
6	0/3	**4k**	Bn	Ph		0	0	0		**5k**	100	

[a] Conditions: 3 equiv (Ph_2PLi/Ph_2PH), THF, −78 °C to rt, 15 min.
[b] SM: starting material.

Then, in accordance with the literature, we thought of performing a nucleophilic addition of chiral phosphine[11] or phospholane oxide,[12] onto acyclic ene-carbamate. We anticipated that, as previously described, a spontaneous migration of the Boc group could occur. Ene-carbamate **4e** bearing a pyridine moiety was chosen as a model. Unfortunately, despite experiments performed in different conditions (*n*-BuLi, THF, −78 °C to rt.[13], or *t*-BuOK, DMSO, 30–40 °C[14]), the desired adduct could not be isolated (Scheme 2).



Scheme 2. Conditions: (i): *n*-BuLi, THF, −78 °C to rt or *t*-BuOK, DMSO, 30–40 °C.

It is also noteworthy that preliminary experiments in this field have shown that the nucleophilic addition of phosphide anion of chiral phosphine borane[15] onto the double of the ene-carbamate was so far unsuccessful.

3. Conclusion

To sum up, we extended the scope of the intermolecular carbolithiation reaction to the nucleophilic addition of phosphide anions onto acyclic ene-carbamates. This methodology allowed a convenient and efficient approach to phosphine-containing α-amino acids bearing quaternary carbon. Unfortunately, so far it has been impossible to induce stereoselectivity during the

nucleophilic addition process by using (−)-sparteine. However, synthesized phosphine-containing compounds could have different relevant uses (phosphine ligands, peptides analogues, development of metal binding group for medical imaging ⋯) and studies are currently being pursued in these fields.

4. Experimental section

4.1. General methods

All non aqueous reactions were carried out in oven or flame-dried glassware under an argon atmosphere, unless otherwise noted. All solvents were reagent grade. THF was distilled from sodium/benzophenone ketyl immediately prior to use. NMR spectra were recorded at 25 °C on multinuclear FT-NMR spectrometer Avance 400 (Bruker) at 400 (^{1}H), 100 (^{13}C), 376.5 (^{19}F) and 162 (^{31}P) MHz. Chemical shifts δ are given in parts per million, shift references are tetramethylsilane for ^{1}H and ^{13}C. ^{13}C and ^{31}P spectra are proton-decoupled. Compounds were visualized by UV irradiation and/or spraying with a solution of potassium permanganate, followed by charring at 150 °C. Chromatography columns were performed on silica gel 60 (230–400 mesh, 0.040–0.063 mm). Melting points (mp [°C]) were taken on samples in open capillary tubes and are uncorrected. The infrared spectra of compounds were recorded on an ATR-Infrared Fourier Transform spectrophotometer. Compounds **3a**, **3b** and **4a** were synthesized according to previously published reports.

4.2. General procedure for the preparation of vinylphosphates (3a–c)

Starting amide **2** (3.7 mmol) was dissolved in dry THF (15 mL) and the mixture was cooled down to −78 °C under argon. A lithium diisopropylamine solution (5.6 mmol, 2 M in THF/n-Heptane) was then added dropwise and the mixture was stirred at −78 °C for 90 min. Subsequently, diphenylchlorophosphate (5.6 mmol) was added. After 2 h at −78 °C, the mixture was quenched with water. The aqueous phase was extracted with 20 mL of EtOAc. Combined organic phases were dried over $MgSO_4$ and evaporated under vacuum. Flash chromatography (silica gel, petroleum ether/EtOAc 1:9) provided pure vinylphosphates **3a**–**c**.

*4.2.1. Tert-butyl benzyl(1-(diphenoxyphosphoryloxy) vinyl)carbamate (**3c**).* Colorless oil. ^{1}H NMR, 400 MHz, ($CDCl_3$) δ 1.42 (9H, s), 4.50 (1H, br s), 4.57 (2H, s), 4.97 (1H, br s), 7.19–7.36 (15H, m). ^{13}C NMR, 100 MHz, ($CDCl_3$) δ 28.3, 51.7, 82.7, 98.2, 120.3, 125.8, 127.6, 128.0, 128.2, 130.0, 137.7, 146.4, 150.6, 153.8. ^{31}P NMR, 162 MHz, ($CDCl_3$) δ −18.7. IR ν_{max} cm^{-1}: 1488, 1193, 1146, 944, 753, 689.

4.3. General procedure (A) for the preparation of acyclic ene-carbamates 4 via Suzuki coupling (see Table 2)

Phosphate **3** (3.2 mmol) was dissolved in degassed THF (10 mL) under argon. Dichloro-bis(triphenylphosphine) palladium (II) (0.32 mmol) was then added and the mixture was degassed and flushed under argon. Boronic acid (8.0 mmol), aqueous sodium carbonate solution (2 M, 3.2 mL), and EtOH (three drops) were added at once. The reaction mixture was then rapidly degassed, flushed under argon and heated at 60 °C for 30 min. After cooling, the reaction mixture was filtered through Celite, and was washed with EtOAc (50 mL). The organic phase was washed with brine, dried over anhydrous $MgSO_4$ and concentrated. Flash chromatography (silica gel, petroleum ether/EtOAc 9:1) afforded the desired pure product.

4.4. General procedure (B) for the synthesis of the ene-carbamates via a Stille cross-coupling (see Table 2)

Phosphate **3** (3.2 mmol) was dissolved in degassed toluene (10 mL) under argon. The dichloro-bis(triphenylphosphine) palladium (II) (0.32 mmol) was added and the mixture was degassed and flushed under argon. 2-tributylstannylpyridine (8.0 mmol) and lithium chloride (6.2 mmol) were added. The reaction mixture was quickly degassed and flushed under argon. The mixture was then heated at 90 °C for a night. Brine (50 mL) and EtOAc (50 mL) were added. The organic phase was separated and the aqueous phase was extracted with 20 mL of EtOAc. Combined organic phases were dried over $MgSO_4$ and evaporated under vacuum. Flash chromatography of the crude (silica gel, petroleum ether then petroleum ether/EtOAc 9:1) provided pure product.

*4.4.1. Tert-butyl 1-(2-fluorophenyl) vinyl(phenyl) carbamate (**4b**).* Colorless solid. Mp(°C): 39–40 °C. ^{1}H NMR, 400 MHz, ($CDCl_3$) δ 1.25 (9H, s), 5.16 (1H, s), 5.42 (1H, s), 7.03–7.20 (3H, m), 7.25–7.42 (6H, m). ^{13}C NMR, 100 MHz, ($CDCl_3$) δ 27.0, 80.3, 113.7, 113.8, 114.9, 115.2, 123.1, 123.2, 124.7, 125.2, 127.9, 128.0, 128.1, 128.5, 128.6, 142.3, 142.4, 142.4, 152.3, 157.9, 160.4. ^{19}F NMR, 376.5 MHz ($CDCl_3$) δ −116.17. IR (neat) ν_{max} cm^{-1}:. 1712, 1365, 1491, 1336, 1218. HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{19}H_{20}NO_2{}^{23}Na$: 336.1375; found 336.1369.

*4.4.2. Tert-butyl 1-(benzo[b]thiophen-2-yl) vinyl (phenyl) carbamate (**4c**).* Yellow solid. Mp(°C): 117–118 °C. ^{1}H NMR, 400 MHz, ($CDCl_3$) δ 1.36 (9H, s), 5.23 (1H, s), 5.69 (1H, s), 7.14–7.17 (1H, m), 7.25–7.34 (5H, m), 7.42–7.45 (2H, m), 7.66–7.70 (1H, m), 7.71 (1H, m). ^{13}C NMR, 100 MHz, ($CDCl_3$) δ 28.1, 81.5, 114.5, 118.5, 121.5, 123.1, 124.8, 124.5, 124.7, 124.9, 125.3, 128.9, 139.4, 139.9, 142.5, 142.7, 142.9, 153.4. IR ν_{max} cm^{-1}: 1711, 1503, 1317, 1288, 1251, 1150. HRMS (ESI) m/z $[M-{}^t\mathrm{Bu}]^+$ calcd for $[C_{17}H_{12}NO_2]$: 294.0589; found 294.0593.

*4.4.3. Tert-butyl 1-(benzofuran-2-yl) vinyl (phenyl) carbamate (**4d**).* Yellow solid. Mp(°C): 120–121 °C. ^{1}H NMR, 400 MHz, ($CDCl_3$) δ 1.39 (9H, s), 5.34 (1H, s), 6.00 (1H, s), 6.70 (1H, s), 7.14–7.55 (9H, m). ^{13}C NMR, 100 MHz, ($CDCl_3$) δ 27.1, 80.4, 103.2, 110.1, 113.2, 120.3, 122.0, 123.9, 124.5, 127.6, 127.7, 137.8, 141.3, 152.4, 152.8, 153.9. IR ν_{max} cm^{-1}: 1705, 1118, 1063, 988, 711. HRMS (ESI) m/z $[M-{}^t\mathrm{Bu}]^+$ calcd for $[C_{17}H_{12}NO_3]$: 278.0817; found 278.0827.

*4.4.4. Tert-butyl phenyl(1-(pyridin-2-yl) vinyl) carbamate (**4e**).* Brown oil. ^{1}H NMR, 400 MHz, ($CDCl_3$) δ 1.26 (9H, s), 5.23 (1H, s), 5.95 (1H, s), 7.11–7.20 (2H, m), 7.29 (2H, dd, J=8.4 Hz), 7.43 (2H, dd, J=0.8, 8.8 Hz), 7.49 (1H, d, J=7.6 Hz), 7.65 (1H, dt, J=1.6, 7.6 Hz), 8.60 (1H, m). ^{13}C NMR, 100 MHz, ($CDCl_3$) δ 27.9, 81.0, 114.4, 120.0, 122.7, 125.3, 125.5, 128.6, 136.5 143.3, 148.2, 149. 2, 153.3, 156.0. IR ν_{max} cm^{-1}: 1707, 1342, 1154, 1100, 746. HRMS (ESI) m/z $[M-{}^t\mathrm{Bu}]^+$ calcd for $[C_{14}H_{11}N_2O_2]$: 239.0821; found 239.0838.

*4.4.5. Tert-butyl 1-phenylvinyl(o-tolyl)carbamate (**4f**).* Yellow oil. ^{1}H NMR, 400 MHz, ($CDCl_3$) δ 1.16 (9H, s), 2.33 (3H, s), 4.57 (1H, s), 5.01 (1H, s), 7.11–7.32 (7H, m), 7.55 (2H, d, J=7.0 Hz). ^{13}C NMR, 100 MHz, ($CDCl_3$) δ 18.2, 27.9, 80.9, 107.6, 126.0, 127.2, 127.6, 128.1, 128.4, 131.1, 135.7, 139.9, 142.5, 149.5, 153.2. IR ν_{max} cm^{-1}: 1709, 1345, 1299, 1163, 768. HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{20}H_{23}NO_2{}^{23}Na$: 332.1626; found 332.1633.

*4.4.6. Tert-butyl 1-(2-fluorophenyl)vinyl(o-tolyl) carbamate (**4g**).* Yellow oil. ^{1}H NMR, 400 MHz, ($CDCl_3$) δ 1.18 (9H, s), 2.31 (3H, s), 4.61 (1H, s), 4.92 (1H, s), 7.01–7.31 (7H, m), 7.47 (1H, t, J=7.7 Hz). ^{13}C NMR, 100 MHz, ($CDCl_3$) δ 27.8, 28.4, 80.9, 109.0, 109.1, 115.5, 115.7, 124.0, 127.1, 127.9, 130.8, 136.2, 141. 9, 143.7, 152.7, 158.5, 160.9. ^{19}F NMR, 376.5 MHz

($CDCl_3$) δ −116.1. IR ν_{max} cm^{-1}: 1709, 1307, 1218, 759. HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{20}H_{23}NO_2F$: 328.1699; found 328.1713.

*4.4.7. Tert-butyl 1-(benzo[b]thiophen-2-yl)vinyl(o-tolyl)carbamate (**4h**).* Yellow solid. Mp(°C): 130 °C. ^1H NMR, 400 MHz, ($CDCl_3$) δ 1.28 (9H, s), 2.37 (3H, s), 4.83 (1H, s), 5.35 (1H, s), 7.12–7.29 (6H, m), 7.42 (1H, s), 7.71 (2H, m). ^{13}C NMR, 100 MHz, (DMSO) δ 18.2, 28.1, 81.1, 111.3, 122.0, 122.7, 124.3, 125.1, 125.3, 127.2, 127.6, 131.4, 135.6, 139.0, 140.0, 142.0, 143.0, 143.3, 152.8. IR ν_{max} cm^{-1}: 1707, 1102, 993, 728. HRMS (ESI) *m*/*z* $[M]^{+\bullet}$ calcdd for $C_{22}H_{23}NO_2S$: 365.1450; found 365.1470.

*4.4.8. Tert-butyl 1-(benzofuran-2-yl)vinyl(o-tolyl)carbamate (**4i**).* Yellow solid. Mp(°C): 110–111 °C. ^1H NMR, 400 MHz, ($CDCl_3$) δ 1.30 (9H, s), 2.38 (3H, s), 4.96 (1H, s), 5.63 (1H, s), 6.83 (1H, s), 7.12–7.31 (6H, m), 7.42–7.56 (2H, m). ^{13}C NMR, 100 MHz, (DMSO) δ 18.1, 28.1, 81.0, 104.4, 111.0, 111.5, 121.8, 123.7, 125.4, 127.2, 127.7, 127.9, 128.9, 131.4, 135.8, 139.7, 141.9, 152.9, 154.3, 154.6. IR ν_{max} cm^{-1}: 1709, 1324, 1108, 994. HRMS (ESI) *m*/*z* $[M\text{-}^tBu]^+$ calcd for $[C_{18}H_{14}NO_3]$: 292.0974; found 292.0953.

*4.4.9. Tert-butyl 1-(pyridin-2-yl)vinyl(o-tolyl)carbamate (**4j**).* Yellow oil. ^1H NMR, 400 MHz, ($CDCl_3$) δ 1.08 (9H, s), 2.27 (3H, s), 4.69 (1H, s), 5.32 (1H, s), 7.06–7.25 (5H, m), 7.45 (1H, m), 7.57 (1H, t, *J*=7.8 Hz), 8.50 (1H, d, *J*=4.7 Hz). ^{13}C NMR, 100 MHz, ($CDCl_3$) δ 17.9, 27.8, 80.7, 109.9, 120.6, 122.5, 126.9, 127.1, 127.1, 130.8, 135.8, 136.2, 142.3, 148.9, 148.9, 152.9. IR ν_{max} cm^{-1}: 1709, 1354, 1158 1082. HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{23}N_2O_2$: 311.1760; found 311.1754.

*4.4.10. Tert-butyl benzyl(1-phenylvinyl)carbamate (**4k**).* Colorless oil. ^1H NMR, 400 MHz, ($CDCl_3$) δ 1.13 (9H, s), 4.62 (2H, s), 4.85 (1H, s), 5.13 (1H, s), 7.11–7.22 (10H, m). ^{13}C NMR, 100 MHz, ($CDCl_3$) δ 27.9, 53.2, 80.4, 109.5, 125.8, 127.1, 127.5, 128.1, 128.2, 128.5, 128.6, 138.7, 138.9, 147.8, 154.7. IR ν_{max} cm^{-1}: 1695, 1366, 1153, 696. HRMS (ESI) *m*/*z* $[M+Na]^+$ calcd for $C_{20}H_{23}NO_2{}^{23}Na$: 332.1627; found 332.1626.

4.5. General procedure for the nucleophilic addition of lithiated phosphine onto acyclic ene-carbamates

Ene-carbamate **4** (0.40 mmol) was dissolved in dry THF (2 mL) and was degassed. The solution was cooled at −78 °C. In a separate dry flask, to a degassed solution of diphenylphosphine (1.20 mmol) in dry THF (2 mL) was added *n*-butyllithium (1.20 mmol, 1.6 M solution in hexanes), which led to the apparition of an intense red color. This red solution was slowly canulated into the first flask cooled at −78 °C. The cold bath was removed, letting the reaction mixture warm up to room temperature for 15 min. The reaction mixture was then quenched with saturated ammonium chloride (5 mL). EtOAc (5 mL) was added. The organic phase was separated and the aqueous phase was extracted with 20 mL of EtOAc. Combined organic phases were dried over $MgSO_4$ and evaporated under vacuum. Flash chromatography of the residue (silica gel, petroleum ether then Petroleum ether/EtOAc 9/1) provided the pure product.

*4.5.1. Tert-butyl 3-(diphenylphosphino)-2-phenyl-2-(phenylamino)-propanoate (**5a**).* Colorless solid. Mp(°C): 120–121 °C. ^1H NMR, 400 MHz, ($CDCl_3$) δ 1.22 (9H, s), 3.42 (2H, ddd, *J*=4.4, 14.1, 26.8 Hz), 5.57 (1H, s), 6.08 (2H, d, *J*=7.6 Hz), 6.47 (1H, dd, *J*=7.2 Hz), 6.79 (2H, dd, *J*=7.2 Hz), 6.97 (2H, dd, *J*=7.2 Hz), 7.07 (3H, m), 7.35 (7H, m), 7.43 (2H, dd, *J*=12 Hz), 7.57 (2H, dd, *J*=12 Hz). ^{13}C NMR, 100 MHz, ($CDCl_3$) δ 27.7, (34.9, *J*=10 Hz), 66.6, 82.8, 115.1, 116.9, 127.0, 127.5, 128.0, 128.1, 128.3, 128.4, 128.5, 128.6, 132.9, 133.0, 133.1, 133.3, 137.3, 139.6, (141.2, 141.3), 144.1, 172.2. ^{31}P NMR, 162 MHz, ($CDCl_3$) δ −22.83. IR ν_{max} cm^{-1}: 1713, 1504, 1288, 1148, 737. HRMS (ESI) *m*/*z* $[M+Na]^+$ calcd for $C_{31}H_{32}NO_2{}^{23}NaP$: 504.2068; found 504.2063.

*4.5.2. Tert-butyl 3-(diphenylphosphino)-2-(2-fluorophenyl)-2-(phenylamino)propanoate (**5b**).* Colorless solid. Mp(°C): 120–121 °C. ^1H NMR, 400 MHz, ($CDCl_3$) δ 1.24 (9H, s), 3.38 (2H, ddd, *J*=4.0, 12.0, 36.0 Hz), 5.13 (1H, s), 6.27 (2H, d, *J*=8 Hz), 6.57 (1H, dd, *J*=8 Hz), 6.89 (3H, m), 7.11–7.33 (6H, m), 7.48 (4H, m), 7.56 (3H, m). ^{13}C NMR, 100 MHz, ($CDCl_3$) 27.5, (Unfortunately, coupling constant with ^{19}F precluded a nice description of the ^{13}C NMR spectrum). ^{19}F NMR, 376.5 MHz ($CDCl_3$) δ −109.9. ^{31}P NMR, 162 MHz, ($CDCl_3$) δ −25.0. IR ν_{max} cm^{-1}: 1720, 1602, 1503, 1281, 1146, 691. HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{31}H_{32}FNO_2P$: 500.2155; found 500.2153.

*4.5.3. Tert-butyl 2-(benzo[b]thiophen-2-yl)-3-(diphenylphosphino)-2-(phenylamino)propanoate (**5c**).* Colorless solid. Mp(°C): 178–179 °C. ^1H NMR, 400 MHz, ($CDCl_3$) δ 1.25 (9H, s), 3.28–3.53 (2H, ddd, *J*=2.6, 14.2, 80.6 Hz), 5.50 (1H, s), 6.30 (2H, d, *J*=7.8 Hz), 6.54 (1H, m), 6.84 (m, 2H), 7.02 (5H, m), 7.25 (6H, m), 7.45 (1H, s), 7.50 (2H, m), 7.68 (2H, dd, *J*=7.6, 21.2 Hz). ^{13}C NMR, 100 MHz, ($CDCl_3$) δ 27.5, (37.4, *J*=10 Hz), (65.2, *J*=20 Hz), 83.4, 115.4, 117.8, 122.2, 123.7, 124.0, 128.0, 128.1, 128.4, 128.4, 128.5, 128.5, (132.8, *J*=10 Hz), (133.0, *J*=10 Hz), 137.1, 138.5, 139.9, 140.4, 144.0, (148.2, *J*=10 Hz), 170.7. ^{31}P NMR, 162 MHz, ($CDCl_3$) δ −23.4. IR ν_{max} cm^{-1}:1715, 1602, 1501, 1433, 1288, 1149, 743. HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{33}H_{33}NO_2PS$: 538.1970; found 538.1964.

*4.5.4. Tert-butyl 3-(diphenylphosphino)-2-(phenylamino)-2-(pyridin-2-yl)propanoate (**5e**).* Colorless solid. Mp(°C): 146–147 °C. ^1H NMR, 400 MHz, ($CDCl_3$) δ 1.27 (9H, s), 3.55 (2H, ddd, *J*=2.4, 16.0, 54.4 Hz), 6.03 (1H, s), 6.21 (2H, d, *J*=8.0 Hz), 6.51 (AH, dd, *J*=7.2 Hz), 6.85 (2H, m), 6.99 (2H, m), 7.10 (4H, m), 7.21 (3H, m), 7.34 (2H, m), 7.42 (1H, m), 7.51 (1H, dt, *J*=2.0, 8.0 Hz), 8.61 (1H, d, *J*=4.8 Hz). ^{13}C NMR, 100 MHz, ($CDCl_3$) δ 27.7, (34.3, *J*=10 Hz), (67.8, *J*=20 Hz), 82.8, 114.7, 117.7, 121.4, 122.6, 128.0, 128.0, 128.1, 128.2, 128.2, 128.3, 128.7, 129.1, 129.3, 130.2, 132.8, 133.0, 133.2, 133.4, 134.4, 134.6, 136.7, 138.2, 139.4, 144.3, 148.6, 159.4, 172.2. ^{31}P NMR, 162 MHz, ($CDCl_3$) δ −25.0. IR ν_{max} cm^{-1}: 3329, 1729, 1600, 1280, 1147, 740. HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{30}H_{31}N_2O_2P$: 483.2182; found 483.2201.

*4.5.5. Tert-butyl 3-(diphenylphosphino)-2-phenyl-2-(o-tolylamino)-propanoate (**5f**).* Clear yellow solid. Mp(°C): 107–108 °C. ^1H NMR, 400 MHz, ($CDCl_3$) δ 1.29 (9H, s), 2.03 (3H, s), 3.46 (2H, ddd, *J*=2.7, 14.2, 73.3 Hz), 5.54 (1H, s), 5.87 (1H, d, *J*=8.04 Hz), 6.45 (1H, t, *J*=7.3 Hz), 6.65 (1H, t, *J*=7.9 Hz), 6.78 (1H, d, *J*=7.9 Hz), 7.98 (2H, m), 7.07, (3H, m), 7.33 (7H, m), 7.42 (2H,), 7.59 (2H, d, *J*=7.9 Hz). ^{13}C NMR, 100 MHz, ($CDCl_3$) δ 17.6, 27.6, 34.2 (*J*=13 Hz), 66.4 (*J*=21.2 Hz), 82.7, 112.8, 116.6, 123.2, 125.7, 126.8, 127.3, 127.6, 127.7, 128.1, 128.2, 128.4, 128.4, 128.5, 129.9, 132.6, 132.8, 132.8, 133.0, 136.3 (*J*=11.0 Hz), 139.7 (*J*=11.8 Hz), 141.2 (*J*=7.0 Hz), 141.7, 172.3. ^{31}P NMR, 162 MHz, ($CDCl_3$) δ −22.6. IR ν_{max} cm^{-1}: 1719, 1280, 1150, 734. HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{32}H_{35}NO_2P$: 496.2413; found 496.2405.

*4.5.6. Tert-butyl 3-(diphenylphosphino)-2-(2-fluorophenyl)-2-(o-tolylamino)propanoate (**5g**).* Colorless solid. Mp(°C): 79–80 °C. ^1H NMR, 400 MHz, ($CDCl_3$) δ 1.26 (9H, s), 1.95 (3H, s), 3.45 (2H, ddd, *J*=2.1, 14.4, 60.0 Hz), 5.18 (1H, s), 6.14 (1H, d, *J*=8.1 Hz), 6.49 (1H, t, *J*=7.3 Hz), 6.70 (1H, t, *J*=7.6H), 6.83 (1H, d, *J*=7.2 Hz), 7.08–7.35 (11H, m), 7.47 (2H, dt, *J*=1.4, 8.0 Hz), 7.57 (1H, t, *J*=7.9 Hz). ^{13}C NMR, 100 MHz, ($CDCl_3$) (Unfortunately, coupling constant with ^{19}F precluded a nice description of the ^{13}C NMR spectrum). ^{31}P NMR, 162 MHz, ($CDCl_3$)

δ −24.3. ^{19}F NMR, 376.5 MHz ($CDCl_3$) δ −109.7. IR ν_{max} cm^{-1}: 1731, 1279, 1150, 741, 695. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{32}H_{34}FNO_2P$: 514.2296; found 514.2311.

*4.5.7. Tert-butyl 1-(benzo[b]thiophen-2-yl)-2-(diphenylphosphino)-ethyl(o-tolyl)carbamate (**5h**).* Brown oil. ^{1}H NMR, 250 MHz, ($CDCl_3$) δ 1.29 (9H, s), 2.02 (3H, s), 3.25–3.65 (2H, ddd, J=4.5, 14.3, 82.8 Hz), 5.49 (1H, s), 6.2 (1H, d, J=8.0 Hz), 6.50 (1H, dt, J=1.0, 7.5 Hz), 6.67 (1H, t, J=7.5 Hz), 6.81 (1H, m), 7.00–7.39 (13H, m), 7.69 (2H, m). ^{13}C NMR, 100 MHz, ($CDCl_3$) δ 17.5, 28.3, 36.5 (J=10 Hz), 65.2 (J=20 Hz), 83.4, 113.2, 117.6, 122.1, 122.3, 123.6, 123.7, 124.0, 126.0, 127.5, 127.8, 127.9, 128.3, 128.5, 128.6, 130.1, 132.7, 132.9, 136.4, 138.6, 139.9, 140.4, 141.9, 148.5., 170.9. ^{31}P NMR, 162 MHz, ($CDCl_3$) δ −23.1. IR ν_{max} cm^{-1}: 1729, 1243, 1045, 694. MS (ESI) m/z $[M+H]^+$ $C_{34}H_{34}NO_2PS$: 552.

*4.5.8. Tert-butyl benzyl 3-(diphenylphosphino)-2-phenyl-2-(o-tolyl-amino)propanoate (**5k**).* Colorless solid. Mp(°C): 150–151 °C. NMR, 400 MHz, ($CDCl_3$) δ 1.27 (9H, s), 2.95 (1H, dt, 5.0, 12.5 Hz), 4.05 (1H, br s), 4.46 (1H, br s), 5.37 (m, 1H), 7.12–7.30 (8H, m), 7.40–7.50 (8H, m). ^{13}C NMR, 100 MHz, ($CDCl_3$) δ 28.3, 32.7, 33.4, 55.1, 59.0, 61.9, 64.7, 127.9, 128.2, 128.5, 128.6, 130.4, 130.5, 130.7, 130.8, 131.6, 138.9, 154.9, 182.4, 209.9. ^{31}P NMR, 162 MHz, ($CDCl_3$) δ 28.5. MS (ESI) m/z $[M+Na]^+$ $C_{33}H_{34}NO_2PNa$: 518.

*4.5.9. Tert-butyl2-(diphenylphosphino)-1-phenylethyl(phenyl)carbamate (**6a**).* Colorless oil. ^{1}H NMR, 400 MHz, ($CDCl_3$) δ 1.34 (9H, s), 2.62 (2H, m), 5.55 (1H, m), 6.87 (2H, m), 7.17–7.49 (18H, m). ^{13}C NMR, 100 MHz, ($CDCl_3$) δ 28.4, 32.4 (J=13.7 Hz), 57.5 (18.1 Hz), 127.1, 127.7, 128.3, 128.4, 128.5, 128, 128.7, 128.8, 128.9, 129.1, 130.2, 130.3, 132.5, 133.4, 139.4, 141.4 (J=5.8 Hz), 155.1. ^{31}P NMR, 162 MHz, ($CDCl_3$) δ −22.8. MS (ESI) m/z $[M+H]^+$ $C_{31}H_{33}NO_2P$: 482.

*4.5.10. Tert-butyl 2-(diphenylphosphoryl)-1-phenylethyl(phenyl)-carbamate (**6b**).* Colorless oil. ^{1}H NMR, 400 MHz, ($CDCl_3$) δ 1.22 (9H, s), 2.78–2.86 (1H, m), 3.36 (1H, m), 5.65 (1H, m), 6.76–6.79 (2H, m), 7.10 (8H, m), 7.3–7.5 (6H, m), 7.5–7.7 (4H, m). ^{13}C NMR, 100 MHz, ($CDCl_3$) δ 28.2, 33.4 (J=69 Hz), 57.1 80.3, 114.3, 126.6, 128.3, 128.5, 129.1, 130.7, 131.5, 133.8, 140.6 (J=8 Hz), 154.4, 171.1. ^{31}P NMR, 162 MHz, ($CDCl_3$) δ 28.6. MS (ESI) m/z $[M+H]^+$ $C_{31}H_{33}NO_3P$: 498.

*4.5.11. Tert-butyl 2-(diphenylphosphoryl)-1-(pyridin-2-yl)ethyl(phenyl)carbamate (**6c**).* Colorless oil. ^{1}H NMR, 400 MHz, ($CDCl_3$) δ 1.32 (9H, s), 3.08 (1H, br s), 3.49–3.57 (1H, m), 5.86–5.93 (1H, m), 6.94 (m, 2H), 7.20–7.70 (16H, m), 8.37 (m, 1H). ^{13}C NMR, 100 MHz, ($CDCl_3$) δ 28.4, 31.3, 32.0, 57.9, 80.9, 122.3, 122.9, 126.5, 128.7, 131.0, 132.0, 140.9, 148.5, 154.5. ^{31}P NMR, 162 MHz, ($CDCl_3$) δ 29.3. MS (ESI) m/z $[M+H]^+$ $C_{30}H_{32}N_2O_3P$: 499.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2009.11.046.

References and notes

1. *Aminophosphonic and Aminophosphonic Acids*; Kuhkar, V. P., Hudson, H. R., Eds.; Wiley: Chichester, UK, 2000.
2. (a) Cowen, B. J.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 10988–10989; (b) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601–610; (c) Holz, J.; Gensow, M.-N.; Zayas, O.; Börner, A. *Curr. Org. Chem.* **2007**, *11*, 61–106; (d) Bunlaksananusorn, T.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3941–3943; (e) Agarkov, A.; Greenfield, S.; Xie, D.; Pawlick, R.; Starkey, G.; Gilbertson, S. R. *Biopolymers (Peptide Science)* **2006**, *84*, 48–73; (f) Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497–537; (g) Knühl, G.; Sennhenn, P.; Helmchen, G. *J. Chem. Soc., Chem. Commun.* **1995**, 1845–1846; (h) Meyer, F.; Laaziri, A.; Papini, A.-M.; Uziel, J.; Juge, S. *Tetrahedron* **2004**, *60*, 3593–3597.
3. (a) *Organophosphorous Chemistry*; The Royal Chemical Society: London, 1969–1983; Vols. 1–15; (b) *Organic Phosphorous Compounds*, 2nd ed.; Kosolapoff, G. M., Maier, L., Eds.; Wiley-Interscience: New York, NY, 1972; Vol. 1.
4. Gilbertson, S. R.; Starkey, G. W. *J. Org. Chem.* **1996**, *61*, 2922–2923.
5. Cottineau, B.; Gillaizeau, I.; Farard, J.; Auclair, M.-L.; Coudert, G. *Synlett* **2007**, 1925–1929.
6. (a) Houk, K. N.; Rondan, N. G.; Schleyer, P. V. R.; Kaufman, E.; Clark, T. *J. Am. Chem. Soc.* **1985**, *107*, 2821–2822; (b) Bailey, W. F.; Khnaolkar, A. D.; Gavaskar, K.; Ovaska, T. V.; Rossi, K.; Thiel, Y.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 5720–5727.
7. Klein, S.; Mareck, I.; Normant, J.-F. *J. Org. Chem.* **1994**, *59*, 2925–2926.
8. N–C acyl migration Rouden, J.; Ragot, A.; Gouault, S.; Cahard, D.; Plaquevent, J.-C.; Lasne, M.-C. *Tetrahedron: Assymmetry* **2002**, *13*, 1299–1305.
9. Structures of **5e**, **5f** and **5k** have been deposited with the Cambridge Crystallographic Data Centre (entries CCDC 748011, 748012 and 748216).
10. The enantiomeric excess of phosphine-containing aminoesters was studied by supercritical fluid chromatography on chiral columns. See West, C.; Bouet, A.; Gillaizeau, I.; Coudert, G.; Lafosse, M.; Lesellier, E. *Chirality* **2009**. doi:10.1002/chir.20735
11. Togni, A.; Breutel, C.; Soares, M. C.; Zanetti, N.; Gerfin, T. *Inorg. Chim. Acta* **1994**, *222*, 213–224.
12. Toffano, M.; Dobrota, C.; Fiaud, J.-C. *Eur. J. Org. Chem.* **2006**, 650–656.
13. Bunlaksananusorn, T.; Knochel, P. *J. Org. Chem.* **2004**, *69*, 4595–4601.
14. Haynes, R. K.; Lam, W. W.-L.; Yeung, L.-L. *Tetrahedron Lett.* **1996**, *37*, 4729–4732.
15. (a) Bauduin, C.; Moulin, D.; Kaloun, E. B.; Darcel, C.; Jugé, S. *J. Org. Chem.* **2003**, *11*, 4293–4301; (b) Jackson, M.; Lennon, I. C. *Tetrahedron Lett.* **2007**, *48*, 1831–1834; (c) Pilkington, C. P.; Zanotti-Gerosa, A. *Org. Lett.* **2003**, *5*, 1273–1275; (d) Oisaki, K.; Zhao, D.; Suto, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2005**, *46*, 4325–4329.