Tetrahedron Letters 51 (2010) 4662–4665

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Thermomorphic fluorous phosphines as organocatalysts for Michael addition reactions

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ARTICLE INFO

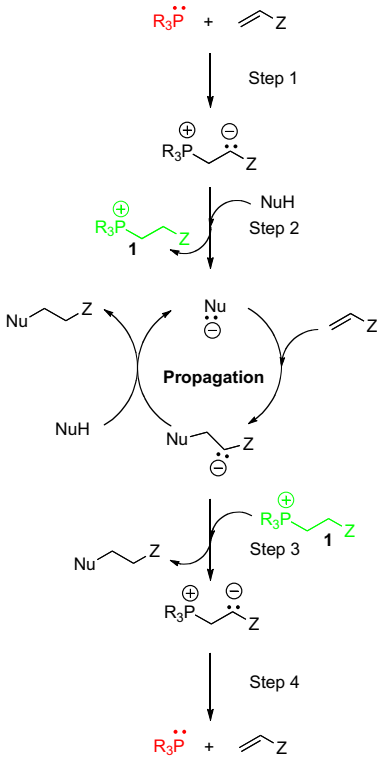
Article history:
Received 6 June 2010
Revised 29 June 2010
Accepted 30 June 2010

ABSTRACT

The fluorous phosphines $P[(CH_2)_mR_{fn}]_3$ ($R_{fn} = (CF_2)_{n-1}CF_3$; m/n = 2/8, 3/8, 3/10) are efficient nucleophilic catalysts of Michael addition reactions. They can be easily recycled based upon their highly temperature-dependent solubilities (thermomorphism), with recovery by simple liquid/solid phase separation. The phosphonium salt formed by reaction of the nucleophilic phosphine with the α,β-unsaturated system appears to be a significant component of the catalyst rest state.

Organocatalysis has become a powerful tool for developing useful new catalytic reactions.[1] Among the advantages of such catalysts are their low toxicities and the intrinsic absence of any heavy-metal-containing waste. Some of us have recently described the excellent activity of phosphines as organocatalysts for conjugate additions of β-dicarbonyl compounds[2a] as well as non-nucleophilic nitrogen-containing species.[2b] This methodology is based upon the nucleophilic attack of the phosphine at the β-position of an electron-deficient alkene, generating a phosphonium β-ylide that triggers subsequent C–C or N–C bond formation (Scheme 1). In a final step, the phosphine is regenerated, thanks to its excellent leaving group properties, and it is quickly oxidized to the corresponding phosphine oxide. This method is an attractive alternative to the traditionally used basic catalysis or neutral metallic conditions. In order to further optimize our procedure, we decided to design a recyclable protocol based on the now well-established concept of fluorous chemistry. This strategy is currently considered, together with ionic liquid, aqueous, and supercritical fluid methodologies, as one of the leading choices for environmentally friendly recycling processes.[3,4]

Since the first report of organic fluorous biphasic catalysis,[5] the synthesis of highly fluorinated phosphines has received much attention mainly due to the fact that they can play valuable roles as ligands of metal complexes,[6] which could then be recovered under biphasic conditions. However, this kind of phosphine has seldom been applied in organocatalysis.[7] Some years ago, some of us described several novel properties of fluorous trialkyl phosphines with the formula $P[(CH_2)_mR_{fn}]_3$ ($R_{fn} = (CF_2)_{n-1}CF_3$).[7a,b] For example, these compounds exhibit highly temperature-dependent solubilities in organic solvents—a type of thermomorphism. This allowed the development of catalyst recycling protocols that did



Scheme 1. Postulated mechanism of phosphine-catalyzed conjugate additions. The red and green species denote possible catalyst rest states.

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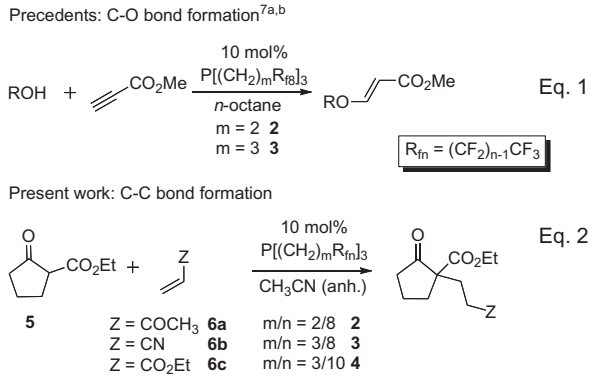
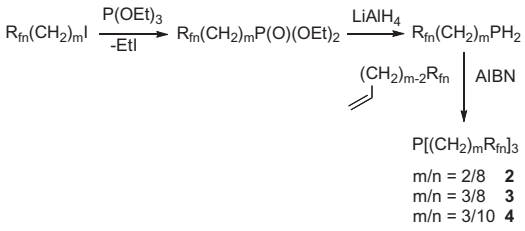
doi:10.1016/j.tetlet.2010.06.136



Scheme 2. Reactions catalyzed by fluorous phosphines.



Scheme 3. Synthesis of phosphines **2**–**4**.

not rely upon fluorous solvents, but rather simple liquid/solid phase separations.

As shown in Eq. 1 of Scheme 2, a series of alcohols could be added to methyl propiolate in good yields, using the fluorous phosphines **2** (m/n = 2/8) and **3** (m/n = 3/8) as catalysts, which could be recycled up to five times. Now we present the application of analogous methodology to the Michael addition reactions shown in Eq. 2 of Scheme 2.

Phosphines **2**, **3**, and **4** (m/n = 3/10) were synthesized using a sequence described previously, which has as a key step an Arbuzov reaction (Scheme 3).[8,9] Alternatively these compounds can be obtained by free radical additions of PH_3 to the corresponding fluorous alkenes $H_2C{=}CH(CH_2)_{m-2}R_{fn}$.[10] The latter route is desirable from the standpoint of atom economy, but we decided to use the former for practical and safety reasons, since PH_3 is a toxic, hazardous, and expensive gas.

As shown in Eq. 2 of Scheme 2, the activities of phosphines **2**–**4** as organocatalysts were screened with the reactions of ethyl 2-oxopentanecarboxylate **5** and several electrophilic alkenes (**6a**–**c**).

Table 1
Michael addition reactions of compound **5** and acceptors **6a**–**c** (Eq. 2, Scheme 2)[a]

Entry	Z	R_3P	t (h)	Conversion[b]
1	$COCH_3$ (**6a**)	**2**	1.5	100
2	$COCH_3$ (**6a**)	**3**	25 min (10 min)	100 (99)
3	$COCH_3$ (**6a**)	**4**	25 min (10 min)	100 (99)
4[c]	$COCH_3$ (**6a**)	Ph_3P	5.5	100
5	CN (**6b**)	**2**	27.5	68
6	CN (**6b**)	**3**	1.5	100
7	CN (**6b**)	**4**	6	100
8	CN (**6b**)	Ph_3P	5.5	100
9	CO_2Et (**6c**)	**2**	27	96
10	CO_2Et (**6c**)	**3**	1.5	100
11	CO_2Et (**6c**)	**4**	3 (1.5)	100 (99)
12	CO_2Et (**6c**)	Ph_3P	21	100

[a] 1 equiv of **5** (0.82 M), 3 equiv of **6**, 10 mol % of R_3P, N_2 atmosphere, refluxing acetonitrile.
[b] Determined by GC as $[A_{product}/(A_{product} + A_{starting\ material})]$.
[c] Room temperature.

Table 2
Recyclability of phosphines **3** and **4** in Michael addition reactions depicted in Eq. 2, Scheme 2[a]

Entry	R_3P	Z	t (h)	Yield[b] (%, five cycles)
1	$[R_{f8}(CH_2)_3]_3P$	$COCH_3$ (**6a**)	10 min	90, 98, >99, 69, 37
2	(**3**)	CN (**6b**)	1.5	78, 72, 68, 61, 31
3		CO_2Et (**6c**)	1.5	>99, 99, 96, 80, 6
4	$[R_{f10}(CH_2)_3]_3P$	$COCH_3$ (**6a**)	10 min	98, >99, >99, 44, 50
5	(**4**)	CN (**6b**)	6	69, 72, 68, 74, 60
6		CO_2Et (**6c**)	1.5	97, 80, 96, 76, 58

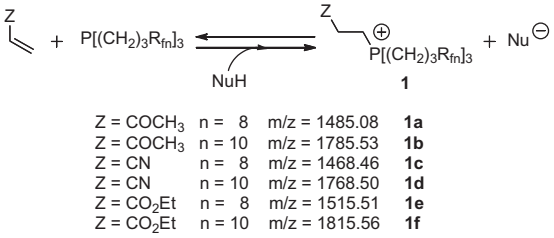
[a] 0.032 mmol of R_3P, 0.4 mL of anhydrous acetonitrile, 0.33 mmol of **5**, 0.99 mmol of **6**, 0.23 mmol of internal standard, N_2 atmosphere, reflux.
[b] Determined by GC versus an internal standard.

In scouting reactions with commercial Ph_3P, various organic solvents were evaluated (acetonitrile, chloroform, tetrahydrofuran, 1,2-dichloroethane, and toluene). Acetonitrile gave the fastest rates, and moreover phosphines **2**, **3**, and **4** exhibited highly temperature-dependent solubilities in this medium.

All reactions were carried out in closed Schlenk tubes in anhydrous acetonitrile at 85–90 °C, using three equivalents of electrophile and 10 mol % of phosphine. The results, depicted in Table 1, demonstrate that fluorous phosphines are excellent catalysts for the Michael additions in Eq. 2, Scheme 2, and in many cases even better than Ph_3P. The length of the perfluorinated R_{fn} segment does not substantially affect the activity of the phosphines, as evidenced in entries 2–3, 6–7, or 10–11. However, the longer $(CH_2)_3$ 'methylene spacer', which increases the basicity and nucleophilicity of the phosphorus, is crucial for obtaining reasonable reaction times. This prompted us to focus upon phosphines **3** and **4** for recycling studies.

To recycle the catalyst, the reaction mixture was cooled to −30 °C. A precipitate formed, and the supernatant was removed by cannula filtration. The catalyst residue was washed with more anhydrous acetonitrile, and then reused.[11] The reaction times and yields for each cycle are summarized in Table 2, with TON values of 7–10 for the initial cycle. These results demonstrate that phosphines **3** and **4** can be recycled successfully, although after the third cycle the yield drops, presumably due to catalyst loss. The R_{f10} phosphine **4** seems to give superior results, as the yields for the fifth cycle are higher than those obtained with the R_{f8} phosphine **3**. Since the solubilities of fluorous compounds decrease as the R_{fn} segments are lengthened, this probably reflects diminished leaching.

The decreases in yields after the third cycle, particularly in the case of phosphine **3**, prompted us to further investigate certain details of these reactions. After each cycle, the solid catalyst residues were separated and the product containing *supernatants* was analyzed by ^{31}P NMR (25 °C). The phosphines **3** or **4** were not detected (–33.6 ppm). However, a unique signal around 37 ppm always appeared in reactions with acrylonitrile **6b** and ethyl acrylate **6c**. In reactions involving methyl vinyl ketone **6a**, more than one signal in the same region (34–37 ppm) was observed. These chemical



Scheme 4. Formation of phosphonium salts **1**.

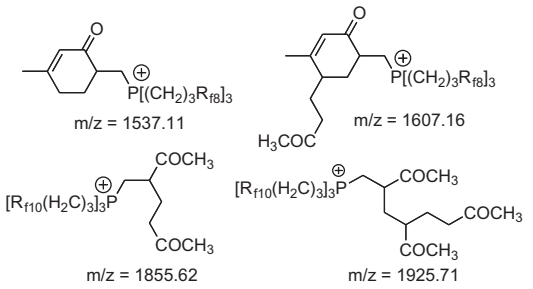


Figure 1. Byproducts in reactions involving methyl vinyl ketone **6a**.

shifts are typical for fluorous phosphonium salts,[12] suggestive of intermediates $ZCH_2CH_2P^+[(CH_2)_3R_{fn}]_3$ (**1**; Scheme 4) according to the mechanism previously proposed (Scheme 1).[2] This hypothesis was supported by FAB$^+$-MS experiments on the crude reaction mixtures. Strong signals were detected for the species of the composition **1a**–**f** (Scheme 4). In the case of methyl vinyl ketone, the extra ^{31}P NMR signals correspond to higher condensation products of the type illustrated in Figure 1, also detected using FAB$^+$-MS. They are derived from aldol and Rauhut–Currier reactions.[13] Finally, after five cycles the filtered solid catalyst residue was analyzed by ^{31}P NMR (C_6D_6 + $CF_3C_6F_{11}$, 25 °C) and only the phosphines **3** and **4** and their respective oxides (minor species) were detected. No appreciable quantities of phosphonium salts were observed, indicating that they remain in solution.

As described earlier, the nucleophilic phosphine initially attacks the β-carbon of the α,β-unsaturated system, generating a phosphonium β-ylide (step 1, Scheme 1) that deprotonates the nucleophile NuH giving the phosphonium salt **1** (step 2, Scheme 1). The conjugate base of the nucleophile Nu: then triggers the propagation steps. Finally, when no more NuH is present in the reaction medium, the phosphine could be recovered from the phosphonium salt **1** (steps 3 and 4, Scheme 1).[2] However, if these last steps of the proposed mechanism are not favorable, the catalyst rest state becomes the phosphonium salt **1** instead of the starting phosphine. According to the above-mentioned ^{31}P NMR and FAB$^+$-MS experiments, it can be concluded that for the reactions in Tables 1 and 2, which involve threefold excesses of the electrophile **6**, fluorous phosphines do not constitute the sole rest state. Since the fluorous phosphonium salts remain soluble in acetonitrile, even at −30 °C, some catalyst loss is unavoidable, rationalizing the decrease in yields after the third cycle. The fact that phosphine **4** gives better recycling results may arise from its greater fluorous character, lowering solubility in acetonitrile, and rendering the equilibrium in Scheme 4 less favorable.

In conclusion, we have described the use of the thermomorphic fluorous phosphines **2**–**4** as organocatalysts to perform Michael addition reactions. However, constitutes a significant portion of the catalyst rest state under the conditions utilized, the phosphonium salt **1**, and **2**–**4** do not play active roles in the propagation steps. Nonetheless, this study has significantly expanded the scope of the reactions for which **2**–**4** can serve as recoverable catalysts or catalyst precursors.

Acknowledgments

Financial support from the Ministerio de Ciencia e Innovación of Spain (Projects CTQ2008-05409-C02-01 and CTQ2005-04968-C02-01 and Consolider Ingenio 2010 (CSD2007-00006)), the DURSI-Generalitat de Catalunya (SGR 2005-00305 and SGR 2009-SGR1441), the Deutsche Forschungsgemeinschaft (DFG, GL 300/3-3), and the Welch Foundation (A-1656) is gratefully acknowledged.

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9. *Synthesis of phosphine* **2**: In a glove box a Schlenk flask was charged with $R_{f8}(CH_2)_2PH_2$[8] (7.06 g, 14.7 mmol), $H_2C{=}CHR_{f8}$[14] (19.7 g, 44.1 mmol, 2.5 equiv), and AIBN (0.200 g, 2.43 mmol). The mixture was stirred at 90 °C, and after 5 h cooled to room temperature. A second charge of AIBN was added. After another 4 h at 90 °C, the sample was cooled, and toluene (40 mL) and perfluoromethylcyclohexane (60 mL) were added. The biphasic mixture was cooled to −30 °C. A white solid precipitated, which was collected on a sintered glass filter and rinsed with cold toluene (2 × 20 mL). The rinses were cooled again and more solid precipitated, which was washed with cold toluene (20 mL). The crops were combined and dried to give **2**[10] (18.0 g, 13.1 mmol, 89%). ^{1}H NMR (C_6D_6 + $CF_3C_6F_{11}$, 300 MHz) δ (ppm): 1.6 (m, 6H), 2.18 (m, 6H); ^{31}P{^{1}H} NMR (C_6D_6 + $CF_3C_6F_{11}$, 121.5 MHz) δ (ppm): −24.7 (s); ^{13}C NMR (C_6D_6 + $CF_3C_6F_{11}$, 75.5 MHz) δ (ppm): 16.8 (m), 28.0 (m).
Synthesis of phosphine **3**: Following the same procedure, $R_{f8}(CH_2)_3PH_2$[8] (1.53 g, 3.1 mmol), $H_2C{=}CHCH_2R_{f8}$[10,15] (3.56 g, 7.7 mmol), and AIBN (0.101 g, 0.6 mmol) were combined. After 19 h, toluene (5 mL) and perfluoromethylcyclohexane (5 mL) were added. The mixture was vigorously stirred, and the toluene layer was separated. The fluorous phase was washed with toluene (ca. 5 mL). The solvent was removed under vacuum outside the glove box to give **3**[10] as a snowy white solid (4.32, 3.1 mmol, 98%). ^{1}H NMR (C_6D_6 + $CF_3C_6F_{11}$, 300 MHz) δ (ppm): 1.20–1.55 (m, 2H), 1.71–1.95 (m, 2H), 2.04–2.3 (m, 2H); ^{31}P{^{1}H} NMR (C_6D_6 + $CF_3C_6F_{11}$, 121.5 MHz) δ (ppm): −33.6 (s); ^{13}C NMR (C_6D_6 + $CF_3C_6F_{11}$, 75.5 MHz) δ (ppm): 16.8 (d, J = 16.7 Hz), 26.8 (d, J = 14.8 Hz), 32.1 (td, J_{C-F} = 22.5 Hz and J_{C-P} = 12.5 Hz).
Synthesis of phosphine **4**: Following the same procedure, $R_{f10}(CH_2)_3PH_2$[16] (1.00 g, 1.7 mmol), $H_2C{=}CHCH_2R_{f10}$[15b,17] (2.40 g, 4.3 mmol), and AIBN (0.058 g, 0.4 mmol) were combined. After 19 h, toluene (5 mL) and perfluoromethylcyclohexane (5 mL) were added. The mixture was vigorously stirred, and the toluene layer was separated. The fluorous phase was washed with toluene (2 × ca. 5 mL). The solvent was removed under vacuum outside the glove box to give **4** as a waxy white solid (2.78, 1.6 mmol, 96%). ^{1}H NMR (C_6D_6 + $CF_3C_6F_{11}$, 300 MHz) δ (ppm): 1.13–1.34 (m, 2H), 1.50–1.90 (m, 2H), 1.95–2.15 (m, 2H); ^{31}P{^{1}H} NMR (C_6D_6 + $CF_3C_6F_{11}$, 121.5 MHz) δ (ppm): −33.6 (s); ^{13}C NMR (C_6D_6 + $CF_3C_6F_{11}$, 75.5 MHz) δ (ppm): 16.2 (m), 26.7 (m), 32.0 (m). Anal. Calcd for $C_{33}H_{18}F_{63}P$: C, 27.30; H, 1.05. Found: C, 27.39; H, 1.14.
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