

1,2-Addition of trialkylaluminium reagents to *N*-diphenylphosphinoylketimines in the absence of any additional reagents†

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Received (in Cambridge, UK) 13th September 2007, Accepted 11th October 2007

First published as an Advance Article on the web 23rd October 2007

DOI: 10.1039/b714161k

Using reactive trialkylaluminium reagents for the 1,2-addition on acetophenone- and benzophenone-derived ketimines, α -tri-substituted amines were obtained in excellent yields up to 99%.

The synthesis of α -trisubstituted amines is of high interest in medicinal chemistry as these compounds inhibit particular biological activity. Some examples for such substrates are the alkaloid *Hemiargan D* (**1**), the aminosquiterpene *Aminobisabolanol* (**2**) as well as the NMDA receptor blocker *Dizocilpine* (**3**) (Fig. 1).^{1–3}

While a variety of α -disubstituted amines can be prepared by addition reactions to aldimines,⁴ the synthesis of α -trisubstituted amines from ketimines is not well established so far (Fig. 2).

Addition of nucleophiles to ketimines is one of the most simple routes for the preparation of α -trisubstituted amines. The synthesis of α -branched amines by 1,2-addition of organometallic reagents is one of the most important reactions in homogeneous catalysis.⁵ In contrast to the well established 1,2-addition of zinc organyls to aromatic ketones,⁶ the application of ketimines as alkyl or aryl group acceptors under similar conditions has proven much more challenging. Recently, Shibasaki and co-workers were able to apply *N*-diphenylphosphinoylketimines in the asymmetric allylation and Mannich-type reaction to obtain α -chiral amines.⁷

The low reactivity of ketimines as well as their rapid isomerization to an unreactive enamine under basic conditions are two important difficulties, which have to be overcome to establish efficient processes for the addition of organometallic reagents.

Trialkylaluminium reagents are of high interest for alkylation since they are commercially available and are used on industrial scale.⁸ Therefore the alkylation of imines by AlR_3 should have great potential for practical applications. Although

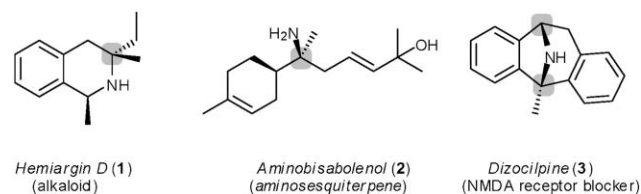


Fig. 1 Biologically active α -trisubstituted amines.

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† Electronic supplementary information (ESI) available: Experimental section and spectroscopic data. See DOI: 10.1039/b714161k

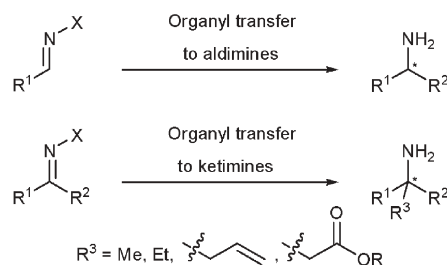


Fig. 2 Synthesis of α -branched amines.

triethylaluminium is a cheap and powerful ethylation reagent for carbon–carbon and carbon–heteroatom double bonds,⁹ it fails to affect imines under standard laboratory conditions.¹⁰

In this report, we explored the 1,2-addition of trialkylaluminium reagents to several acetophenone- or benzophenone-derived *N*-diphenylphosphinoylketimines in the absence of any additional reagents (Fig. 3).¹¹

We examined both triethyl- and trimethylaluminium under several reaction conditions.† In the presence of AlEt_3 or AlMe_3 , electron-neutral and electron-rich imines undergo 1,2-addition in almost quantitative yields. At room temperature the reaction proceeds without the use of any additional reagents. Thus alkylation of a variety of ketimines could be accomplished at room temperature.

First, we investigated the necessary amount of trialkylaluminium reagent to achieve good yields for the activated model

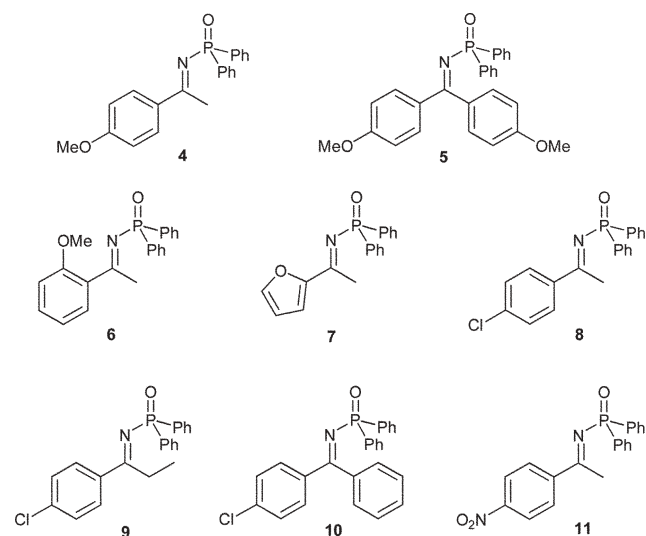


Fig. 3 *N*-Diphenylphosphinoylketimines used.

Table 1 1,2-Addition of trialkyl aluminium reagents to *N*-diphenylphosphinoylketimines

Entry	Reagent	R ¹	R ²	Metal organyl	T/°C	Time/h	Yield (%)
1a	8	4-ClC ₆ H ₄	CH ₃	3 equiv. AlEt ₃	25	0.5	74
1b	8	4-ClC ₆ H ₄	CH ₃	4 equiv. AlEt ₃	25	0.5	88
1c	8	4-ClC ₆ H ₄	CH ₃	5 equiv. AlEt ₃	25	0.5	98
2	4	4-MeOC ₆ H ₄	CH ₃	3 equiv. AlEt ₃	25	20	99
3a	8	4-ClC ₆ H ₄	CH ₃	4 equiv. AlEt ₃	0	1	65
3b	8	4-ClC ₆ H ₄	CH ₃	4 equiv. AlEt ₃	−25	1	7
4a	8	4-ClC ₆ H ₄	CH ₃	4 equiv. ZnEt ₂ ^a	0	16	—
4b	11	4-O ₂ NC ₆ H ₄	CH ₃	4 equiv. ZnEt ₂ ^b	−25	16	—
5	6	2-MeOC ₆ H ₄	CH ₃	4 equiv. AlEt ₃	25	72	—
6	7	Furyl	CH ₃	4 equiv. AlEt ₃	25	16	99
7	8	4-ClC ₆ H ₄	CH ₃	4 equiv. AlMe ₃	25	24	92
8	9	4-ClC ₆ H ₄	CH ₂ CH ₃	6 equiv. AlMe ₃	25	20	63
9	10	4-ClC ₆ H ₄	C ₆ H ₅	4 equiv. AlMe ₃	25	20	84
10	5	4-MeOC ₆ H ₄	4-MeOC ₆ H ₄	4 equiv. AlEt ₃	25	16	87
11	10	4-ClC ₆ H ₄	C ₆ H ₅	4 equiv. AlEt ₃	25	20	62

^a Addition of 0.1 equiv. (*R_p,S*)-paracyclophane-ligand in *n*-hexane, ^b Addition of 1.0 equiv. *N,N*-dimethylethanolamine in toluene.

compound **8** (Table 1, entries 1a–c). We found that at least 3 to 4 equiv. of the aluminium reagent are needed to obtain yields up to 88%. However to obtain a quantitative yield within short reaction times, 5 equiv. of the corresponding aluminium organyl are required. Lowering the nucleophile loading to 3 equiv. required prolonged reaction times (20 h) to achieve full conversion with quantitative yield (Table 1, entry 2).

Since the temperature is an important factor for the selectivity of a chemical process we investigated the temperature limit for this model reaction (Table 1, entries 3a and 3b).

When the reaction was performed at −25 °C or below (see ESI†) the starting material was recovered in almost (near to) quantitative yield. The choice of solvents also has to be considered, since there is no reaction taking place in coordinating solvents *e.g.* Et₂O or THF at temperatures around 0 °C or slightly below. Additionally the considered imines are unreactive towards zinc organyls as we tried to convert them with diethylzinc and different *N,O*-additives (Table 1, entries 4a and 4b).

The scope of the optimized reaction is shown in Table 1, entries 5–11. The 1,2-addition to electron-rich ketimines such as **6** (entry 5), the furyl-derivative **7** (entry 6) as well as **5** (entry 10) proceed in good to excellent yields up to 99%, although longer reaction times are necessary (16–20 h). The 1,2-addition to the electron-poor ketimines **8**, **9** and **10** (Table 1, entries 7–9) initiated by trimethylaluminium proceed in up to 92% yield. Due to the poor reactivity of trimethylaluminium the reaction needs to be run 24 h for completion.

It is worth mentioning that all products yielded by 1,2-addition are of high purity without further purifications as flash-chromatography or recrystallization. We explored this favourable circumstance by a modified quenching procedure by saturated K/Na-tartrate solution.

In summary we explored the first 1,2-addition of trialkylaluminium organyls to *N*-diphenylphosphinoylketimines to obtain α -trisubstituted amines in high yields up to 99%.

In our ongoing studies we are exploring this reaction to be carried out in an asymmetric fashion to achieve enantiomerically pure products.

This work has been supported by the BMBF (WING program) and the Landesgraduiertenförderung (fellowship to R. R.).

Notes and references

† *General procedure* for the addition of trialkylaluminium reagents to *N*-diphenylphosphinoylketimines: Under a dry argon atmosphere, the corresponding imine (0.5 mmol) was dissolved in 1.0 mL of dry toluene and stirred for 0.5 h at room temperature to give a homogeneous solution. Then AlEt₃ or AlMe₃ (4.00 mmol), used as a 1 M solution in toluene or *n*-hexane, was added under argon and stirred for the indicated time. After all of the starting material was consumed, the mixture was quenched by addition of methanol and saturated solution of K/Na-tartrate. The aqueous layer was extracted with ethyl acetate (3 × 5 mL), dried over MgSO₄ and filtered. The filtrate was concentrated under reduced pressure. The products were obtained in high purity without further purification.

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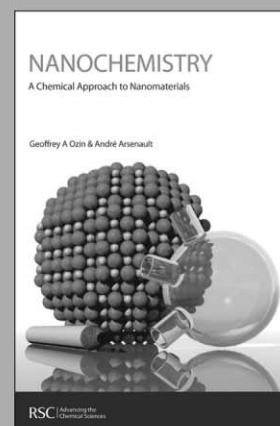
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