2-Phenallyl as a versatile protecting group for the asymmetric one-pot three-component synthesis of propargylamines†

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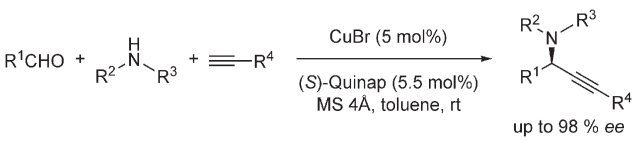
2-Phenallyl was found to be a versatile protecting group of primary amines for the asymmetric one-pot three-component synthesis of propargylamines which leads to enantiomeric excess of up to 96%; it can be easily removed with a palladium(0)-catalyzed allylic substitution using 1,3-dimethylbarbituric acid as a nucleophile.

Protecting groups play an important role in synthetic organic synthesis.[1] The allyl group is widely used for the protection of alcohols, amines and carboxylic acids. Allyl groups are stable under both acidic and basic conditions, but can easily be removed by palladium-catalyzed substitution reactions with various nucleophiles.[2] Recently, we[3] and others[4] have reported a three-component asymmetric reaction of a terminal alkyne, an aldehyde and a secondary amine using copper(I) bromide/Quinap[5] as the catalytic system leading to enantiomerically enriched propargylamines (Scheme 1).

In the course of our studies, we have investigated various amine protecting groups. While dibenzylamine leads to the highest enantioselectivity (Scheme 2, **1a**, 98% *ee*), the removal of this group was not possible under mild conditions. Hydrogenation of the dibenzyl protected propargylamines under standard conditions[6] led to the reduction of the triple bond. Oxidative methods like CAN- or DDQ-oxidations also failed to remove chemoselectively the benzyl group. Extensive decomposition of the starting propargylamine was observed. The allyl group itself can be used as a protecting group during the propargylamine synthesis, but lower % *ee* are obtained.[7] To increase the enantioselectivity of this reaction, we have investigated the influence of the steric hindrance of the allylic amine. The use of diallylamine in a test reaction led to the desired amine **1b** in only 90% *ee* compared to 98% *ee* obtained by the reaction with dibenzylamine (product **1a**). Increasing the steric hindrance by the use of bis(methallyl)amine led to the corresponding product **1c** in 92% *ee*. Finally, the use of



Scheme 1 Asymmetric three-component synthesis of propargylamines.

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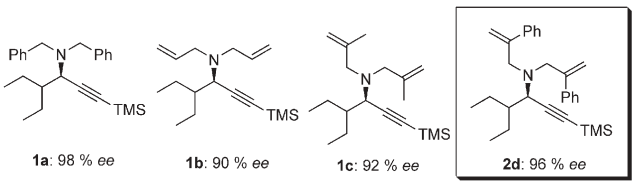


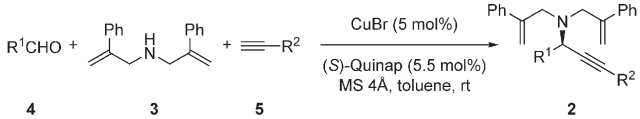
Scheme 2 Influence of the steric demand in the allyl protecting group.

bis(phenallyl)amine[8] **3** provides the propargylamine **2d** in 96% *ee*, which exhibits still a synthetically useful level of selectivity (see Scheme 2).

Furthermore, the bis(phenallyl)amine is easily prepared from commercially available starting materials using standard protocols. Thus, allylic bromination[9] of α-methylstyrene using NBS at 160 °C furnished the substituted allyl bromide in 70% yield. Nucleophilic substitution with potassium phthalimide in DMF followed by reductive cleavage with hydrazine in MeOH yielded the primary allylamine in 66% yield over two steps.[10] Condensation with 2-phenallyl bromide led to bis(phenallyl)amine **3** in 70% yield.

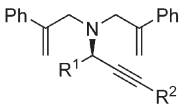
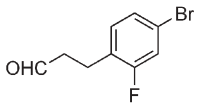
In order to examine the scope of this new protecting group in the three-component reaction, several aldehydes **4** and alkynes **5** were reacted with **3** in the presence of CuBr/Quinap leading to bis(phenallyl)-protected propargylamines **2** (Scheme 3 and Table 1).

With trimethylsilylacetylene (**5a**), branched and unbranched aliphatic aldehydes lead to the corresponding propargylamines **2a–f** in good yields and enantioselectivities (entries 1–6, Table 1). The selectivity increases with the steric demand of the aldehyde. Valeraldehyde (**4a**) leads to the product **2a** with 84% *ee* (entry 1), isovaleraldehyde (**4b**) gives **2b** with 90% *ee* (entry 2) and 2-ethylbutyraldehyde (**4d**) produces the highest selectivity leading to **2d** with 96% *ee* (entry 4). Aldehydes bearing a cyclic substituent like cyclopropyl- and cyclohexylcarbaldehyde afford the desired propargylamines **2e–f** in 79–82% yield and 84 and 92% *ee*, respectively (entries 5–6). The functionalized dihydrocinnamaldehyde **4g** also leads to the desired product **2g** in good yield but somewhat lower enantioselectivity (75% *ee*, entry 7). Phenylcinnamaldehyde **4h** also participates in the reaction leading to propargylamine **2h** with 81% *ee* (entry 8). Benzaldehyde (**4i**)

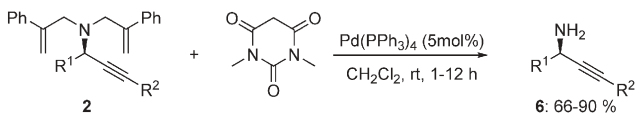


Scheme 3 Asymmetric three-component synthesis of bis(phenallyl)-protected propargylamines.

Table 1 Asymmetric three-component synthesis of bis(phenallyl)-protected propargylamines

Nr.	Aldehyde **4**	Alkyne **5**	Propargylamine **2**	Yield[a](%)	*ee*[b](%)
	R^1CHO	$\equiv-R^2$			
1	**4a**: R^1: *n*-Bu	**5a**: R^2: TMS	**2a**: R^1: *n*-Bu; R^2: TMS	86	84
2	**4b**: R^1: *i*-Bu	**5a**	**2b**: R^1: *i*-Bu; R^2: TMS	67	90
3	**4c**: R^1: *i*-Pr	**5a**	**2c**: R^1: *i*-Pr; R^2: TMS	79	86
4	**4d**: R^1: *s*-Pent	**5a**	**2d**: R^1: *s*-Pent; R^2: TMS	67	96
5	**4e**: R^1: *c*-Pr	**5a**	**2e**: R^1: *c*-Pr; R^2: TMS	79	84
6	**4f**: R^1: *c*-Hex	**5a**	**2f**: R^1: *c*-Hex; R^2: TMS	82	92
					
7	**4g**	**5a**	**2g**: R^1: $(CH_2)_2$(2-F-4-Br-C_6H_3); R^2: TMS	75	75
8	**4h**: R^1: $(C_6H_5)_2C=CH$	**5a**	**2h**: R^1: $(C_6H_5)_2C=CH$; R^2: TMS	83	81
9	**4i**: R^1: Ph	**5a**	**2i**: R^1: Ph; R^2: TMS	67	34
10	**4j**: R^1: 3-benzothiophene	**5a**	**2j**: R^1: 3-benzothiophene; R^2: TMS	58	84
11	**4f**	**5b**: R^2: *n*-Bu	**2k**: R^1: *c*-Hex; R^2: *n*-Bu	82	68
12	**4d**	**5c**: R^2: Ph	**2l**: R^1 *s*-Pent; R^2: Ph	71	70

[a] Isolated yield of analytically pure product. [b] Enantiomeric excess determined by HPLC using Chiracel OD-H column (*n*-heptane : *i*-PrOH).



Scheme 4 Deprotection leading to primary amines **6**.

leads to the product **2i** with only 34% *ee* (entry 9), whereas 3-benzothiophenaldehyde (**4j**) gives the desired propargylamine **2j** in 84% *ee* (entry 10). Likewise, other alkynes can be reacted, but the selectivities are lower. Therefore, reaction of 1-hexyne (**5b**) with cyclohexanecarbaldehyde (**4g**) and bis(phenallyl)amine (**3**) leads to the propargylamine **2k** in 82% yield and 68% *ee* (entry 11). Reaction of 2-ethylbutyraldehyde (**4d**) with amine **3** and phenylacetylene (**5c**) gives the propargylamine **2l** in 71% yield and 70% *ee* (entry 12).

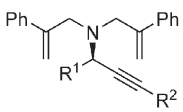
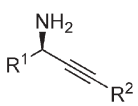
For the product **1b** derived from diallylamine, both allyl groups are readily removed by Guibé's method.[2a] We have observed that the more sterically hindered methallyl group (**1c**) needs more forcing conditions (heating to 60 °C) to achieve full deprotection. In contrast, the bis(phenallyl) groups could be removed efficiently in CH_2Cl_2 at room temperature leading to the corresponding primary propargylamines **6** (Scheme 4, Table 2).

Various propargylamines **2** can be converted to the corresponding primary amines **6**. Thus, the propargylamines **2d–e** can be transformed to the amines **6a** and **6b** in 66–75% yield (entries 1–2, Table 2). Interestingly, the allyl-substituted propargylamine **2h** derived from phenylcinnamaldehyde undergoes a selective cleavage of the phenallyl groups leading to the product **6c** in 83% yield (entry 3).

Likewise the phenyl-substituted amine **2i** was subjected to the deprotection procedure and furnished the benzylamine **6d** in 77% yield (entry 4). Finally, deprotection also takes place with the phenylacetylene-substituted amine **2l** leading to **6e** in very good yield (90%, entry 5).

In summary, we have developed an efficient protecting group for the synthesis of chiral primary propargylamines.

Table 2 Removal of the phenallyl groups leading to primary amines **6**

Nr.	Propargylamine **2**	Primary amine **6**	Yield[a](%)	*ee*(%)
				
1	**2d**: R^1: *s*-Pent; R^2: TMS	**6a**: R^1: *s*-Pent; R^2: TMS	66	96
2	**2e**: R^1: *c*-Pr; R^2: TMS	**6b**: R^1: *c*-Pr; R^2: TMS	75	84
3	**2h**: R^1: $(C_6H_5)_2C=CH$; R^2: TMS	**6c**: R^1: $(C_6H_5)_2C=CH$; R^2: TMS	83	81
4	**2i**: R^1: Ph; R^2: TMS	**6d**: R^1: Ph; R^2: TMS	77	34
5	**2l**: R^1: *s*-Pent; R^2: Ph	**6e**: R^1: *s*-Pent; R^2: Ph	90	70

[a] Isolated yield of analytically pure product.

Bis(phenallyl)amine is easily prepared and leads to good enantioselectivities (up to 96% *ee*) in the one-pot three-component synthesis of propargylamines. Furthermore, it can be removed using a Pd^0-catalyzed allylic substitution with dimethylbarbituric acid leading to chiral primary propargylamines in good yields. This new protecting group should find numerous applications for the preparation of sensitive amines since the deprotection occurs under very mild conditions.

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Notes and references

1 P. J. Kocienski, *Protective Groups*, Thieme, Stuttgart, 3rd edn., 2003.
2 (*a*) For the deprotection using 1,3-dimethylbarbituric acid, see: F. Garro-Helion, A. Merzouk and F. Guibé, *J. Org. Chem.*, 1993, **58**, 6109; (*b*) for the deprotection using thiosalicylic acid, see: S. Lemaire-Audoire, M. Savignac and J. P. Genêt, *Tetrahedron Lett.*, 1995, **36**, 1267; S. Lemaire-Audoire, M. Savignac, C. Dupuis and J. P. Genêt, *Bull. Soc. Chim. Fr.*, 1995, **132**, 1157; (*c*) for the deprotection using sulfinic acids, see: M. Honda, H. Morita and I. Nagakura, *J. Org. Chem.*, 1997, **62**, 8932.
3 (*a*) N. Gommermann, C. Koradin, K. Polborn and P. Knochel, *Angew. Chem., Int. Ed.*, 2003, **42**, 5763; (*b*) N. Gommermann and P. Knochel, *Chem. Commun.*, 2004, **20**, 2324; (*c*) H. Dube, N. Gommermann and P. Knochel, *Synthesis*, 2004, **12**, 2015.
4 (*a*) C. M. Wei and C.-J. Li, *J. Am. Chem. Soc.*, 2003, **125**, 9584; (*b*) S. Sakaguchi, T. Kubo and Y. Ishii, *Angew. Chem., Int. Ed.*, 2001, **40**, 2534; (*c*) L. Shi, Y.-Q. Tu, M. Wang, F.-M. Zhang and C.-A. Fan, *Org. Lett.*, 2004, **6**, 1001; (*d*) C. M. Wei and C.-J. Li, *J. Am. Chem. Soc.*, 2002, **124**, 5638; (*e*) C. M. Wei, Z. G. Li and C.-J. Li, *Org. Lett.*, 2003, **5**, 4473; (*f*) for the preparation of propargylic alcohols see: D. E. Frantz, R. Faessler and E. M. Carreira, *J. Am. Chem. Soc.*, 2000, **122**, 1806.
5 (*a*) J. M. Valk, G. A. Whitlock, T. P. Layzell and J. M. Brown, *Tetrahedron: Asymmetry*, 1995, **6**, 2593; (*b*) E. Fernandez, K. Maeda, M. W. Hooper and J. M. Brown, *Chem. Eur. J.*, 2000, **6**, 1840.
6 W. H. Hartung and R. Simonoff, *Org. React.*, 1953, **VII**, 263.
7 (*a*) C. Koradin, K. Polborn and P. Knochel, *Angew. Chem., Int. Ed.*, 2002, **114**, 2651; (*b*) C. Koradin, N. Gommermann and P. Knochel, *Chem. Eur. J.*, 2003, **9**, 2797.
8 During the preparation of this manuscript, the 2-phenallyl group was described first by Barluenga, using *tert*-butyllithium for deprotection: J. Barluenga, F. J. Fananás, R. Sanz, C. Marcos and J. M. Ignacio, *Chem. Commun.*, 2005, 933.
9 For the preparation of [1-(bromomethyl)vinyl]benzene, see: S. F. Reed, *J. Org. Chem.*, 1965, **30**, 3258.
10 (*a*) For the preparation of phenallylamine, see: N. De Kimpe and D. De Smaele, *Tetrahedron*, 1995, **51**, 6465; (*b*) I. A. McDonald, J. M. Lacoste, P. Bey, M. G. Palfreyman and M. Zreika, *J. Med. Chem.*, 1985, **28**, 186.