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Microwave-assisted synthesis of allylic amines: considerable rate acceleration in the hydrozirconation–transmetalation–aldimine addition sequence †

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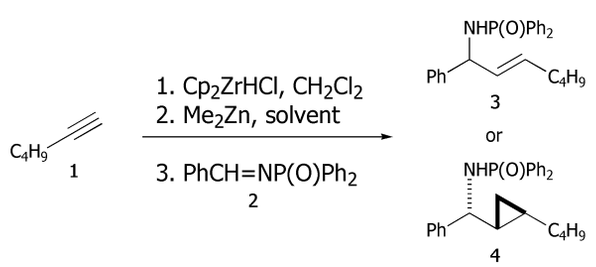
The hydrozirconation of alkynes with zirconocene hydrochloride and the dimethylzinc-mediated addition of alkenylzirconocenes to diphenylphosphinoyl imines can be greatly accelerated with microwave irradiation, resulting in a convenient and rapid one-pot process for the preparation of synthetically useful allylic amines.

Allylic amines are valuable building blocks for organic and medicinal chemists and can be easily transformed into 1,2-amino alcohols and α-amino acids. We have recently reported the preparation of functionalized allylic and *C*-cyclopropyl amines *via* addition of alkenylzirconocenes to diphenylphosphinoyl imines in the presence of dimethylzinc. The allylic amide **3** is formed in an *in situ* protocol from alkyne **1** and imine **2** in toluene, whereas *C*-cyclopropylalkylamide **4** is the major product in CH_2Cl_2 (Scheme 1).[1] Hydrozirconation[2] is a mild method for the selective preparation of functionalized organometallics and its compatibility with a wide variety of common protecting groups represents a considerable advantage of these species over traditional organometallic reagents. The intermediate alkenylzirconocenes have been used in Pd(0)-mediated coupling reactions[3] and in nucleophilic additions to a number of common electrophiles.[4] A drawback of the method shown in Scheme 1 is that overall reaction times can easily exceed 12 h, since both hydrozirconation and imine addition of the intermediate vinyl zinc reagent are often slow even at room temperature. In recent years microwaves have found an increasing number of applications in organometallic chemistry and drug discovery.[5,6] We have now found that alkenylzirconocene and -zinc species are surprisingly stable in the microwave environment under elevated temperature and pressure and thus offer another opportunity for a synthetically advantageous use of this technology.



Scheme 1 One-pot synthesis of allylic and *C*-cyclopropylalkylamines.

† Electronic supplementary information (ESI) available: experimental procedures and ^1H and ^{13}C NMR spectra for all new compounds. See http://www.rsc.org/suppdata/ob/b3/b316741k/

Our preliminary studies immediately revealed a large rate acceleration for the Zr⟶Zn methodology in the preparation of allylic amines using microwave irradiation. Under our original conditions,[1] the hydrozirconation of **1** was performed in CH_2Cl_2; however, this proved to be a poor solvent for the alkenylzirconocene addition and led to considerable concomitant *C*-cyclopropylalkylamine formation. While toluene was the preferred solvent for the nucleophilic imine addition, hydrozirconation in toluene was prohibitively slow: hydrozirconation of 4-octyne at room temperature in toluene did not reach completion even after 48 h. Fortunately, microwave irradiation greatly accelerated this process, and for all alkynes tested thus far, including functionalized, non-functionalized, internal and terminal substrates, hydrozirconation was complete in toluene within 5 min at *ca.* 100 °C with a power setting of 100–150 W. Conventional heating at 100 °C in toluene also accelerated the reaction but was accompanied by significant (~25–30%) side product formation and discoloring of the reaction mixture. Since toluene is a rather transparent solvent for microwave radiation, we hypothesize that dipolar zirconocene and zinc complexes are predominantly responsible for absorption of microwave energy, and that a dielectric heating mechanism is operative. Rate acceleration is particularly effective when the polarity is enhanced from ground to transition state.[7]

In a typical protocol, Schwartz reagent was suspended in dry toluene and treated with terminal or internal alkyne. The reaction mixture was heated in a single-mode microwave reactor,[8] providing a clear yellow to orange solution of alkenyl–zirconium complex. Upon optimization of the conditions with 1-hexyne and 4-octyne, we found that the conversion was complete in 45 s based on GC analysis. Unsymmetrical internal alkynes produced a mixture of regioisomeric alkenes after hydrozirconation with Cp_2ZrHCl and quenching; the kinetically controlled reaction only slightly favoured the isomer derived from addition of the zirconium atom at the carbon bearing the sterically least demanding substituent. In order to improve this ratio, an excess of Cp_2ZrHCl and elevated temperatures were used to reach thermodynamic equilibrium, which generally provides a much greater preference for the least substituted zirconium complex.[2,9] The regioselectivity of hydrozirconation in toluene under microwave conditions was studied in more detail for the cyclohexyl/alkyl-substituted alkynes **5** and **6** (Table 1). Despite the notable difference in the steric bulk of the two triple bond substituents, the observed regioselectivity was poor in the presence of 1 equivalent of Cp_2ZrHCl (Entry 1, 2). While these alkynes were rapidly hydrozirconated in toluene at 100 °C, and favorable ratios were achieved in the presence of a slight excess of reagent (Entry 3), this temperature led to a discoloring of the solution and a

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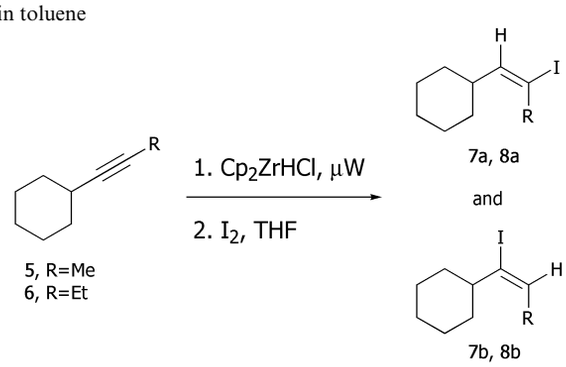
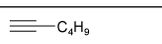
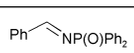
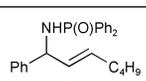
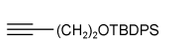
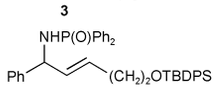
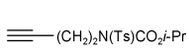
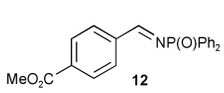
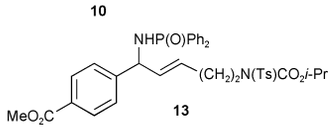
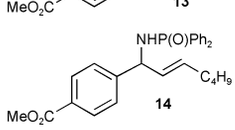
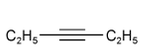
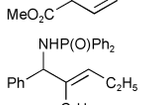
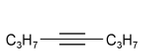
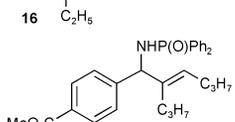
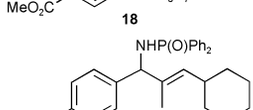
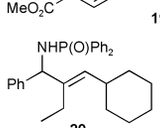
Table 1 Regioselective hydrozirconation in toluene



Entry	R	Eq. Cp_2ZrHCl	Time (min)	Temp (°C) [a]	**7a**, **7b** or **8a**, **8b** [b]
1	Et	1.0	30	60	2.0 : 1
2	Et	1.0	30	100	2.2 : 1
3	Et	1.25	30	100	14 : 1
4	Et	1.5	30	60	3.0 : 1
5	Et	1.5	60	60	3.5 : 1
6	Et	2.0	30	60	>20 : 1
7	Me	2.0	30	60	>20 : 1

[a] Microwave power set at 150 W. [b] Ratio determined by ^{1}H NMR integration of the crude reaction mixture; yields for entries 6 and 7 were essentially quantitative.

Table 2 Microwave-accelerated condensation of alkynes and imines to give allylic amides

Entry	Alkyne	Imine	Allylic amide	Method [a]	Yield (%) [b]
1	 **1**	 **2**	 **3**	A	73
2	 **9**	**2**	 **10**	A	62
3	 **11**	 **12**	 **13**	B	80
4	**1**	**12**	 **14**	B	95
5	 **15**	**2**	 **16**	C	77
6	 **17**	**12**	 **18**	C	74
7	**5**	**12**	 **19**	D	60
8	**6**	**2**	 **20**	D	63

[a] Method A: i) Cp_2ZrHCl (1.5 eq.), alkyne (1.6 eq.), μW 60 °C (150 W), 5 min, ii) Me_2Zn (1.5 eq.), −78 °C to 0 °C, iii) imine, μW 100 °C (150 W), 5 min; Method B: i) Cp_2ZrHCl (1.7 eq.), alkyne (1.5 eq.), μW 80 °C (75 W), flash heating, ii) Me_2Zn (1.5 eq.), −78 °C to 0 °C, iii) imine, μW 100 °C (150 W), flash heating; Method C: i) Cp_2ZrHCl (1.7 eq.), alkyne (1.5 eq.), μW 100 °C (100 W), flash heating, ii) Me_2Zn (1.5 eq.), −78 °C to 0 °C, iii) imine, μW 100 °C (150 W), flash heating; Method D: i) Cp_2ZrHCl (2 eq.), **5** or **6** (1 eq.), μW 60 °C (150 W), 30 min, ii) **5** or **6** (1 eq.), μW 60 °C (150 W), 15 min, iii) Me_2Zn (1 eq.), −78 °C to 0 °C, iv) imine, μW 100 °C (150 W), 15 min; [b] Yield of isolated products based on imines.

poor yield in the subsequent imine addition reaction. Under optimum conditions, hydrozirconation of unsymmetrical internal alkynes was accomplished with 2.0 eq. of Cp_2ZrHCl at 60 °C in 30 min (Table 1, Entries 6, 7). Accordingly, slightly longer reaction times in the microwave are necessary for achieving thermodynamic equilibrium and high regioselectivity for

unsymmetrical internal alkynes, compared to terminal and symmetrical internal alkynes.

A series of alkynes and imines were subjected to the optimized accelerated reaction conditions in the microwave (Table 2). The hydrozirconation products of terminal (Entries 1–4) and symmetrical internal alkynes (Entries 5–6) underwent rapid addition (1–5 min) to imines in the presence of dimethylzinc. Under conventional conditions,[1] terminal alkenylzirconocenes were more reactive than complexes derived from internal alkynes. Under microwave conditions, the reaction rates for both species were comparable. The highest rate increase in the imine addition was observed for Entries 3–6. These examples were performed using the flash heating mode, which led to complete conversion in <1 min.[10] Perhaps due to the short reaction times, the elevated temperatures used in these experiments did not cause the same level of decomposition products compared to the conventional approach, and purification by chromatography on SiO_2 was simplified. All allylic amides were isolated in good to excellent yields. Not unexpectedly, unsymmetrical internal alkynes were found to be the least reactive toward imine addition and required up to 15 min reaction time at 100 °C; however, with these substrates complete conversion was not accomplished even after 24 h under conventional conditions. The advantages of the microwave methodology lie both in the significant time savings of the domino process as well as the increased convenience of carrying out both hydrozirconation and imine addition in a single reaction environment using a non-chlorinated solvent.

In summary, we have developed an expedient new protocol for allylic amine formation using a microwave-based strategy. Hydrozirconation as well as transmetalation to zinc and imine addition steps are greatly accelerated and toluene can now serve as a reaction solvent throughout the entire process. Studies directed towards the application of this technology to the generation of libraries of allylic and *C*-cyclopropylalkylamides are currently under way in our laboratories and will be reported in due course.

Acknowledgements

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