

Platinum(II)-catalyzed intermolecular hydroamination of monosubstituted allenes with secondary alkylamines†

Kristina L. Toups and Ross A. Widenhoefer*

Received (in College Park, MD, USA) 8th December 2009, Accepted 6th January 2010

First published as an Advance Article on the web 16th January 2010

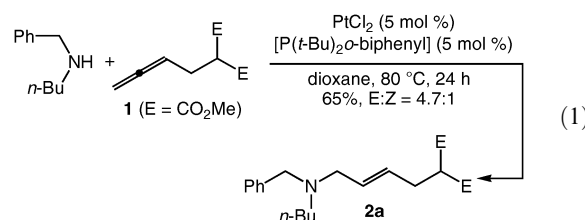
DOI: 10.1039/b925859k

A 1 : 1 mixture of (dppf)PtCl₂ and AgOTf (5 mol%) catalyzed the intermolecular hydroamination of monosubstituted allenes with secondary alkylamines at 80 °C to form allylic amines in good yield with selective formation of the *E*-diastereomer.

The transition metal-catalyzed addition of the N–H bond of an amine across a C–C multiple bond represents an attractive and atom economical approach to the synthesis of functionalized amines.¹ Despite prolonged effort in this area, many of the possible permutations of catalytic hydroamination remain poorly developed. As one example, the intermolecular hydroamination of allenes with alkylamines remains problematic, which is unfortunate as this transformation represents a potentially expedient approach to the synthesis of allylic amines. Group IV complexes catalyze the intermolecular hydroamination of allenes with alkylamines at elevated temperatures but form imines rather than allylic amines.² Palladium(II) complexes catalyze the intermolecular hydroamination of allenes with alkyl amines, but these transformations are of extremely limited scope.³ More recently, cationic gold(I) phosphine⁴ and cyclic (alkyl)(amino)carbene^{5,6} complexes have been applied to the intermolecular hydroamination of allenes with secondary alkylamines. However, the former method was restricted to morpholine as a nucleophile while the latter required forcing conditions (130–165 °C) with monosubstituted allenes and/or simple dialkyl amines. Here we report an effective Pt(II)-catalyzed protocol for the intermolecular hydroamination of monosubstituted allenes with secondary alkylamines.

We have previously employed neutral platinum(II) mono(phosphine) complexes as catalysts for the intramolecular hydroamination of unactivated alkenes with secondary alkyl amines.⁷ Furthermore, Panunzi *et al.* have shown that alkylamines react with the platinum(II) π -allene complex (PPh₃)PtCl₂(η^2 -H₂C=C=CMe₂) to form zwitterionic platinum σ -alkenyl complexes (PPh₃)PtCl₂(η^1 -Me₂C=CCH₂NR₃) that react with HCl to form allylic ammonium chloride salts.⁸ Together these steps constitute a potential catalytic cycle for allene hydroamination. For these reasons, we targeted neutral platinum mono(phosphine) complexes as catalysts for the intermolecular hydroamination of allenes with alkylamines. Initial experiments were encouraging, and treatment of benzyl

n-butyl amine with dimethyl 2,3-butadienylmalonate (**1**; 2 equiv.) catalyzed by a 1 : 1 mixture of PtCl₂ and P(*t*-Bu)₂*o*-biphenyl (5 mol%) in dioxane at 80 °C for 24 h led to isolation of allylic amine **2a** in 65% yield as a 4.7 : 1 mixture of *E*–*Z* isomers (eqn (1)). Unfortunately, subsequent modification of ligand led to no improvement in either the yield or the diastereoselectivity of hydroamination.



As an alternative to neutral mono(phosphine) complexes, we targeted cationic platinum bis(phosphine) complexes as catalysts for allene hydroamination. Although ultimately successful, an initial experiment employing benzyl *n*-butyl amine, **1** (2 equiv.), and a catalytic 1 : 1 mixture of (dppp)PtCl₂ [dppp = 1,3-bis(diphenylphosphino)propane] and AgOTf led to no detectable formation of **2a** (Table 1, entry 1). The effect of the natural bite angle (β_n)⁹ of a bidentate phosphine ligand on the efficiency and/or selectivity of transition metal-catalyzed transformations is well documented.¹⁰ For this reason, we evaluated the efficiency of platinum-catalyzed conversion of **1** to **2a** as a function of phosphine bite angle. The effect was dramatic, and the yield of **2a** increased from 0% to 88% as β_n increased from 91° to $\geq 108^\circ$,¹¹ although the *E*–*Z* selectivity followed no discernable trend (Table 1, entries 1–7). From this group of complexes, we targeted (dppf)PtCl₂ [dppf = 1,1'-bis(diphenylphosphino)ferrocene] and (Nixantphos)PtCl₂ [Nixantphos = 4,6-bis(diphenylphosphino)phenoxazine] for further evaluation, owing to the favorable combination of yield and diastereoselectivity realized with these precatalysts. Optimization with respect to solvent revealed that toluene provided higher yield of **2a** without significant deterioration of diastereoselectivity (Table 1, entries 10 and 11).‡§

Employment of (dppf)PtCl₂ or (Nixantphos)PtCl₂ as precatalysts allowed for the efficient hydroamination of allene **1** with a range of secondary alkylamines. The former generally provided superior yields and reaction of **1** with benzyl methyl amine, di-*n*-butyl amine, diethyl amine, morpholine, piperidine, or pyrrolidine catalyzed by a 1 : 1 mixture of (dppf)PtCl₂ and AgOTf in toluene at 80 °C led to isolation of the corresponding allylic amines **2b–2g** in $\geq 78\%$ yield with ≥ 7.6 : 1 *E*–*Z* diastereoselectivity (Table 2, entries 1–6). Alternatively, reaction of **1** with dibenzyl amine catalyzed by (Nixantphos)PtCl₂–AgOTf

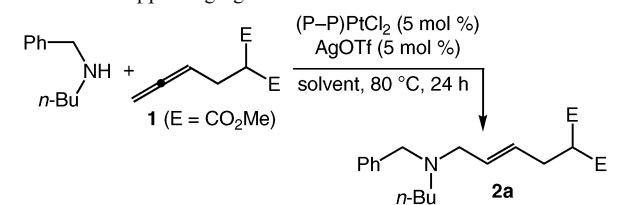
French Family Science Center, Duke University, Durham, NC, USA.

E-mail: rwidenho@chem.duke.edu; Fax: +1-919-6601605;

Tel: +1-919-6601533

† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data, and scans of NMR spectra (35 pages). See DOI: 10.1039/b925859k

Table 1 Platinum(II)-catalyzed hydroamination of dimethyl 2,3-butadienylmalonate (**1**; 2 equiv.) with benzyl *n*-butyl amine as a function of supporting ligand and solvent



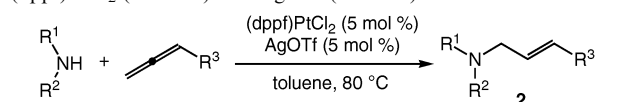
Entry	P-P	$\beta_n^{a/\circ}$	Solvent	Yield ^b (%)	<i>E</i> : <i>Z</i> ^c
1	dppp	91	Dioxane	0	—
2	biphep	92	Dioxane	22	7.0:1
3	binap	93	Dioxane	27	4.1:1
4	dppf	99	Dioxane	70	11:1
5	DPEphos	104	Dioxane	79	5.6:1
6	xantphos	108	Dioxane	88	5.0:1
7	Nixantphos	114	Dioxane	86	6.5:1
8	dppf	99	Methanol	20	17:1
9	Nixantphos	114	Methanol	85	7.8:1
10	dppf	99	Toluene	81	10:1
11	Nixantphos	114	Toluene	91	6.7:1

^a Bite angle data taken from ref. 11. ^b Isolated material of $\geq 95\%$ purity. ^c *E/Z* ratio determined by ¹H NMR analysis of the purified reaction mixture.

led to isolation of **2h** in 66% yield as a 6.9 : 1 mixture of *E-Z* diastereomers (Table 2, entry 7). In addition, a number of aliphatic and aromatic monosubstituted allenes including *n*-octyl-, cyclohexyl-, benzyl-, phenyl-, and 2-naphthylallene underwent efficient hydroamination with benzyl *n*-butyl amine in the presence of (dppf)PtCl₂-AgOTf to form the corresponding allylic amines **2i-2m** in good yield with ≥ 15 : 1 *E-Z* diastereoselectivity (Table 2, entries 8–12). Neither 1,1- nor 1,3-disubstituted allenes underwent efficient intermolecular hydroamination with benzyl *n*-butyl amine under these conditions.

Guided by the precedents of Panunzi *et al.*^{8,12} and others^{13–16} we propose a mechanism for the platinum-catalyzed hydroamination of allenes with secondary alkylamines initiated by chloride abstraction from (P-P)PtCl₂ with AgOTf to initially form the cationic platinum amine complex **I** (Scheme 1).¹⁴ Displacement of the amine ligand of **I** with free allene would form cationic platinum π -allene complexes **II**. Although a number of platinum(II) π -allene complexes are known,^{15,16} complexes of monosubstituted allenes are not among them and hence, the preferred binding mode of monosubstituted allenes to Pt(II) is not known. However, platinum π -allene complexes are known to undergo intramolecular exchange of all four possible allene π -faces, presumably *via* an η^1 -allene intermediate or transition state.^{16,17} Therefore, preferential outer-sphere addition of amine to the unsubstituted allene terminus of platinum π -allene isomer *cis*-**II** would lead to selective formation of platinum σ -alkenyl complex (*Z*)-**III**. A control experiment ruled out *Z-E* isomerization of the allylic amine under reaction conditions.[¶] Protonolysis of the Pt-C bond of (*Z*)-**III** could occur through a number of pathways. As one possibility, deprotonation of the ammonium moiety of (*Z*)-**III** with free amine followed by intermolecular protonolysis of the Pt-C bond of the resulting neutral

Table 2 Intermolecular hydroamination of monosubstituted allenes (2 equiv.) with secondary alkylamines catalyzed by a mixture of (dppf)PtCl₂ (5 mol%) and AgOTf (5 mol%) in toluene at 80 °C



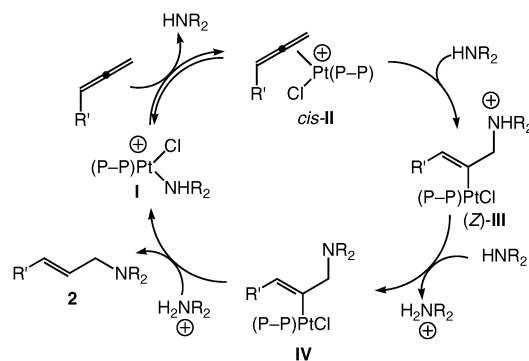
Entry	Amine	Allene	Time/h	Product	Yield ^a (%)	<i>E</i> : <i>Z</i> ^b
1	Ph-CH ₂ -NH-Me	1	24	2b	86	10:1
2	X = O	1	24	2c	89	7.8:1
3	X = CH ₂	1	24	2d	78	7.6:1
4	Cyclohexyl-NH	1	24	2e	78	8.4:1
5	R = <i>n</i> -Bu	1	24	2f	82	17:1
6	R = Et	1	24	2g	86	9.6:1
7 ^c	R = Bn	1	24	2h	66	6.9:1
8	R = <i>n</i> -octyl		48	2i	93	15:1
9	R = Cy		48	2j	89	32:1
10	R = Bn		42	2k	73	39:1
11	R = Ph		38	2l	99	>50:1
12	R = 2-naphthyl		40	2m	86	>50:1

^a Yields refer to isolated material of $>95\%$ purity. ^b *E/Z* ratio determined by ¹H NMR analysis of the purified reaction mixture. ^c (Nixantphos)PtCl₂ employed as precatalyst.

σ -alkenyl complex **IV** with ammonium salt would release allylic amine **2** with regeneration of **I** (Scheme 1).

In summary, we have developed a platinum(II)-catalyzed protocol for the intermolecular hydroamination of monosubstituted allenes with secondary alkylamines to form allylic amines in good yield with selective formation of the *E*-diastereomer. We are currently working toward the development of more general and more effective hydroamination protocols that employ alkylamines as nucleophiles.

Acknowledgement is made to the NIH (GM-080422) for support of this research. KLT was supported in part through a Pharmacological Sciences Training Program fellowship.



Scheme 1

Notes and references

‡ Experimental procedure: a suspension of (dppf)PtCl₂ (8.2 mg, 0.010 mmol), AgOTf (2.6 mg, 0.010 mmol), ferrocene (3.7 mg, 0.020 mmol; internal standard), benzyl *n*-butyl amine (36 μL, 33 mg, 0.20 mmol) and **1** (74 mg, 0.40 mmol) in toluene (0.4 mL) was heated at 80 °C for 24 h. Column chromatography of the crude reaction mixture (SiO₂ pretreated with Et₃N; hexanes–EtOAc = 9 : 1) gave **2a** (pale yellow oil, 56 mg, 81%) as a 10 : 1 mixture of *E* and *Z* diastereomers. § Control experiments ruled out the significant contribution of acid- or silver-catalyzed pathways to the intermolecular hydroamination of **1** and benzyl *n*-butyl amine (see ESI†). ¶ Treatment of a 3.9 : 1 *E*–*Z* mixture of **2b** with a catalytic 1 : 1 mixture of (dppf)PtCl₂ and AgOTf in toluene at 80 °C for 24 h led to no detectable change in the *E*/*Z* ratio.

- 1 (a) T. E. Müller, K. C. Hultsch, M. Yus, F. Foubelo and M. Tada, *Chem. Rev.*, 2008, **108**, 3795; (b) R. A. Widenhoefer and X. Han, *Eur. J. Org. Chem.*, 2006, 4555; (c) F. Pohlki and S. Doye, *Chem. Soc. Rev.*, 2003, **32**, 104; (d) S. Hong and T. J. Marks, *Acc. Chem. Res.*, 2004, **37**, 673.
- 2 (a) P. J. Walsh, A. M. Baranger and R. G. Bergman, *J. Am. Chem. Soc.*, 1992, **114**, 1708; (b) J. S. Johnson and R. G. Bergman, *J. Am. Chem. Soc.*, 2001, **123**, 2923; (c) R. O. Ayinla and L. L. Schafer, *Inorg. Chim. Acta*, 2006, **359**, 3097.
- 3 (a) M. Al-Masum, M. Meguro and Y. Yamamoto, *Tetrahedron Lett.*, 1997, **38**, 6071; (b) L. Besson, J. Goré and B. Cazes, *Tetrahedron Lett.*, 1995, **36**, 3857.
- 4 N. Nishina and Y. Yamamoto, *Synlett*, 2007, 1767.
- 5 X. Zeng, M. Soleilhavoup and G. Bertrand, *Org. Lett.*, 2009, **11**, 3166.
- 6 See also: V. Lavallo, G. D. Frey, B. Donnadieu, M. Soleilhavoup and G. Bertrand, *Angew. Chem., Int. Ed.*, 2008, **47**, 5224.
- 7 (a) C. F. Bender and R. A. Widenhoefer, *J. Am. Chem. Soc.*, 2005, **127**, 1070; (b) C. F. Bender, W. B. Hudson and R. A. Widenhoefer, *Organometallics*, 2008, **27**, 2356.
- 8 A. De Renzi, B. Di Blasio, A. Panunzi, C. Pedone and A. Vitagliano, *J. Chem. Soc., Dalton Trans.*, 1978, 1392.
- 9 C. P. Casey and G. T. Whiteker, *Isr. J. Chem.*, 1990, **30**, 299.
- 10 (a) C. P. Casey, G. T. Whiteker, M. G. Melville, L. M. Petrovich, J. A. Gavney and D. R. Powell, *J. Am. Chem. Soc.*, 1992, **114**, 5535; (b) L. A. van der Veen, P. H. Keeven, G. C. Schoemaker, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, M. Lutz and A. L. Spek, *Organometallics*, 2000, **19**, 872; (c) M. Iwamoto and S. Yuguchi, *J. Org. Chem.*, 1966, **31**, 4290; (d) Y. Kawabata, T. Hayashi and I. Ogata, *J. Chem. Soc., Chem. Commun.*, 1979, 462; (e) T. Hayashi, Y. Kawabata, T. Isoyama and I. Ogata, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 3438; (f) I. del Rio, C. Claver and P. W. N. M. van Leeuwen, *Eur. J. Inorg. Chem.*, 2001, 2719; (g) E. Drent and P. H. M. Budzelaar, *Chem. Rev.*, 1996, **96**, 663; (h) B. C. Hamann and J. F. Hartwig, *J. Am. Chem. Soc.*, 1998, **120**, 7369; (i) T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi and K. Hirotsu, *J. Am. Chem. Soc.*, 1984, **106**, 158; (j) T. Hayashi, M. Konishi and M. Kumada, *Tetrahedron Lett.*, 1979, **20**, 1871; (k) M. Kranenburg, P. C. J. Kamer and P. W. N. M. van Leeuwen, *Eur. J. Inorg. Chem.*, 1998, 25.
- 11 (a) M. Birkholz, Z. Freixa and P. W. N. M. van Leeuwen, *Chem. Soc. Rev.*, 2009, **38**, 1099; (b) M. Ogasawara, K. Yoshida and T. Hayashi, *Organometallics*, 2000, **19**, 1567.
- 12 (a) A. De Renzi, A. Panunzi, M. Scalone and A. Vitagliano, *J. Organomet. Chem.*, 1980, **192**, 129; (b) A. De Renzi, P. Ganis, A. Panunzi, A. Vitagliano and G. Valle, *J. Am. Chem. Soc.*, 1980, **102**, 1722.
- 13 (a) A. De Renzi, B. Di Blasio, G. Morelli and A. Vitagliano, *Inorg. Chim. Acta*, 1982, **63**, 233; (b) J. R. Briggs, C. Crocker, W. S. McDonald and B. L. Shaw, *J. Chem. Soc., Dalton Trans.*, 1981, 575.
- 14 (a) K. Pignat, J. Vallotto, F. Pinna and G. Strukul, *Organometallics*, 2000, **19**, 5160; (b) Y. Kataoka, O. Matsumoto and K. Tani, *Organometallics*, 1996, **15**, 5246.
- 15 (a) T. G. Hewitt and J. J. De Boer, *J. Chem. Soc. A*, 1971, 817; (b) H. C. Clark and L. E. Manzer, *J. Am. Chem. Soc.*, 1973, **95**, 3812; (c) J. R. Briggs, C. Crocker, W. S. McDonald and B. L. Shaw, *J. Chem. Soc., Dalton Trans.*, 1981, 121.
- 16 (a) K. Vrieze, H. C. Volger, M. Gronert and A. P. Praat, *J. Organomet. Chem.*, 1969, **16**, P19; (b) K. Vrieze, H. C. Volger and A. P. Praat, *J. Organomet. Chem.*, 1970, **21**, 467.
- 17 For examples of similar rearrangements see: (a) F. L. Bowden and R. Giles, *Coord. Chem. Rev.*, 1976, **20**, 81; (b) R. Ben-Shoshan and R. Pettit, *J. Am. Chem. Soc.*, 1967, **89**, 2231.