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Enantioselective Iridium-Catalyzed Allylic Substitutions with Hydroxamic Acid Derivatives as N-Nucleophiles

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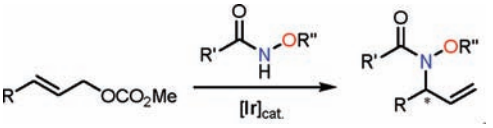
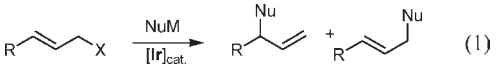
ABSTRACT



Enantioselective Ir-catalyzed allylic aminations with hydroxamic acid derivatives are described. Catalysts were prepared in situ from $[Ir(cod)Cl]_2$ or $[Ir(dbcot)Cl]_2$, a phosphoramidite and base. In addition, pure (π-allyl)Ir complexes containing cod or dbcot as auxiliary ligands were used. Very high degrees of regio- and enantioselectivity were achieved. The reaction products were transformed into piperidine derivatives suited as precursors for aza-sugars.

Transition metal catalyzed asymmetric allylic substitutions have been intensely investigated over several decades.[1] Over the past few years, the iridium-catalyzed reaction has become increasingly important as a method for the synthesis of branched allylic compounds from monosubstituted allylic derivatives, usually allylic carbonates (eq 1). In its presently most often applied version, catalysts are (π-allyl)Ir complexes of cyclometalated phosphoramidites that are used in pure form or generated in situ.[2]



(1)

Recently we became interested in exploring this method for the preparation of *N*-allylated hydroxylamines. These can be regarded as *N*-protected allylamines; however, they are of interest themselves in natural products chemistry,[3] for example, as precursors of *N*-hydroxy aza-sugars,[4] antibiotics,[5] and peptidomimetics.[6]

Hydroxylamine derivatives have been probed in various Pd-catalyzed allylic substitutions.[7] Asymmetric catalysis with these nucleophiles was only investigated by Takemoto et al., using Pd- and Ir-catalyzed allylic substitutions.[8] For the latter reactions a catalyst prepared from the tridentate ligand **Pybox** and $[Ir(cod)Cl]_2$ was used.

(1) Reviews covering the whole field: (a) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258–297. (b) Helmchen, G.; Kazmaier, U.; Förster, S. In *Catalytic Asymmetric Synthesis*, 3rd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2010; pp 497–641.

(2) (a) Helmchen, G.; Dahnz, A.; Dübon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675–691. (b) Helmchen, G. In *Iridium Complexes in Organic Synthesis*; Oro, L. A., Claver, C., Eds.; Wiley-VCH: Weinheim, 2009; pp 211–250. (c) Hartwig, J. F.; Stanley, L. M. *Acc. Chem. Res.* **2010**, *43*, 1461–1475.

(3) *The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids*, Vol. 2; Rappoport, Z., Liebman, J. E., Eds.; Wiley: Chichester, 2011.

(4) Racine, E.; Bello, C.; Gerber-Lemaire, S.; Vogel, P.; Py, S. *J. Org. Chem.* **2009**, *74*, 1766–1769.

(5) (a) Umezawa, K.; Ikeda, Y.; Kawase, O.; Naganawa, H.; Kondo, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1550–1553. (b) Berge, J. M.; Houge-Frydrych, C. S. V.; Jarvest, R. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2521–2523.

(6) Li, X.; Wu, Y.-D.; Yang, D. *Acc. Chem. Res.* **2008**, *41*, 1428–1438.

(7) (a) Imada, Y.; Nishida, M.; Kutsuwa, K.; Murahashi, S.-I.; Naota, T. *Org. Lett.* **2005**, *7*, 5837–5839. (b) Murahashi, S.-I.; Imada, Y.; Taniguchi, Y.; Kodera, Y. *Tetrahedron Lett.* **1988**, *29*, 2973–2976. (c) Genet, J. P.; Thorimbert, S.; Mallart, S.; Kardos, N. *Synthesis* **1993**, 321–324. (d) Genet, J. P.; Thorimbert, S.; Touzin, A.-M. *Tetrahedron Lett.* **1993**, *34*, 1159–1162. (e) Öhler, E.; Kanzler, S. *Synthesis* **1995**, 539–543. (f) Johns, A. M.; Liu, Z.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7259–7261.

(8) (a) Miyabe, H.; Matsumura, A.; Moriyama, K.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 4631–4634. (b) Miyabe, H.; Yoshida, K.; Yamauchi, M.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 2148–2153.

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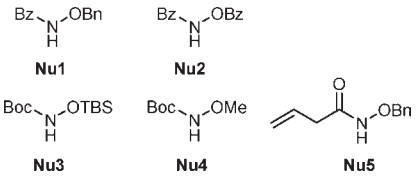
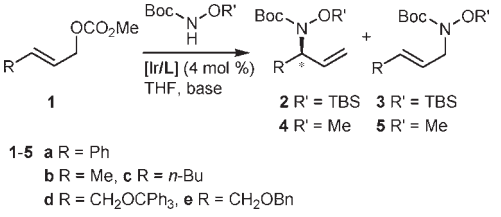


Figure 1. Hydroxamic acid derivatives used as N-pronucleophiles in allylic substitutions.

While the Takemoto group successfully probed a range of hydroxylamine derivatives as O-nucleophiles, only the N-nucleophiles **Nu1** and **Nu2** (Figure 1) were investigated with a few highly reactive arylallyl phosphates (X = $OPO(OEt)_2$) as substrates, which gave moderate selectivity except in one case (R = 1-naphthyl).[8a]

Our own investigation commenced with experiments using *O*-benzyl- and *O*-methylhydroxylamine as nucleophiles, which did not give satisfactory results. Next hydroxamic acid derivatives were considered with the following conditions in mind: (a) The reaction must be feasible with aliphatic and functionalized substituents R. (b) The pronucleophiles should be sufficiently acidic to allow the substitution to be run with allylic carbonates as substrates under "salt-free" conditions, i.e., directly with the pronucleophiles rather than their salts.[9] (c) The protecting groups at O and/or N should be removable selectively under mild conditions.

Scheme 1. Ir-Catalyzed Allylic Substitutions with Hydroxamic Acid Derivatives **Nu3** and **Nu4** as Pronucleophiles



The first nucleophile successfully probed was **Nu3**. This compound was introduced as a pronucleophile for conjugate additions by MacMillan et al.[10] Accordingly, the salt-free conditions should be applicable. Indeed, reactions with a representative set of allylic carbonates **1** (Scheme 1) proceeded smoothly with remarkably high regio- and excellent enantioselectivity.[11] The catalysts were prepared

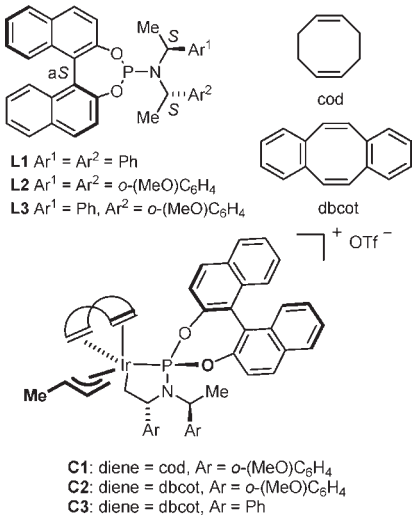
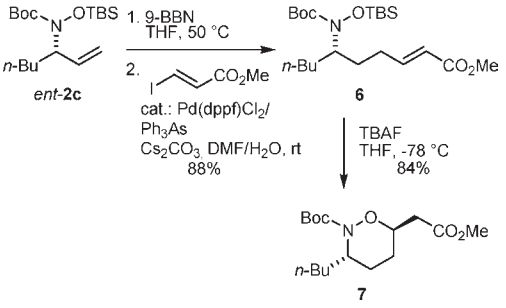


Figure 2. Phosphoramidite ligands, achiral auxiliary ligands, and (π-allyl)Ir complexes used in this work.

in situ by adding the base TBD (1,5,7-triazabicyclo-[4.4.0]dec-5-ene)[12] to a mixture of $[Ir(cod)Cl]_2$ and a phosphoramidite;[13] phosphoramidites **L2** and **L3** (Figure 2), introduced by Alexakis, gave particularly good results.[14] With other nucleophiles (see below) isolated (π-allyl)Ir complexes **C1**–**C3** were additionally used.[15]

Scheme 2. Synthesis of a Chiral Tetrahydro-1,2-oxazine



To indicate possible uses of the substitution products and as a test of O-deprotection, the reaction sequence described in Scheme 2 was carried out. Hydroboration of **2c** with 9-BBN followed by a Suzuki–Miyaura reaction with methyl (*E*)-3-iodo-acrylate gave the enoate **6** in 88% yield. Treatment of **6** with TBAF at −78 °C effected O-deprotection and oxa-Michael addition to give the tetrahydro-1,2-oxazine **7** in 84% yield as a single stereoiso-

(9) (a) Weihofen, R.; Tverskoy, O.; Helmchen, G. *Angew. Chem., Int. Ed.* **2006**, *45*, 5546–5549. (b) Spiess, S.; Berthold, C.; Weihofen, R.; Helmchen, G. *Org. Biomol. Chem.* **2007**, *5*, 2357–2360. (c) Singh, O. V.; Han, H. *Tetrahedron Lett.* **2007**, *48*, 7094–7098.

(10) (a) Chen, J. K.; Yoshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328–9329. (b) Simmons, B.; Walji, A. M.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 4349–4353.

(11) The assignment of the absolute configuration is based on a rule on the configurational course of the Ir-catalyzed allylic substitution, which was always found valid so far (ref 2).

(12) It is very important that this compound be carefully dried (see Supporting Information).

(13) Review: Teichert, J. F.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 2486–2528.

(14) (a) Polet, D.; Alexakis, A. *Org. Lett.* **2005**, *7*, 1621–1624. (b) Polet, D.; Alexakis, A.; Tissot-Croset, K.; Corminboeuf, C.; Ditrich, K. *Chem.—Eur. J.* **2006**, *12*, 3596–3609.

mer.[16] This procedure supplements syntheses of dihydro-1,2-oxazines from *O*,*N*-diallylhydroxamic acids via ring closing metathesis.[17] Tetrahydro-1,2-oxazines are valuable intermediates, for example, for syntheses of pyrrolidine alkaloids.[18]

Table 1. Ir-Catalyzed Allylic Substitutions with the Pronucleophile **Nu3** [a]

entry	substrate	L*	time (h)	yield (%)[b]	b/l[c]	ee (%)[d]
1	**1a**	**L2**	3	83	98:2	99
2	**1a**	**L3**	20	65	98:2	99
3	**1c**	**L2**	2.5	90	98:2	99
4	**1c**	**L3**	43	56	98:2	98
5[e]	**1d**	**L2**	2.5	72	97:3	96
6[e]	**1d**	**L3**	16	74	96:4	97

[a] Reactions were carried out with THF as solvent at rt; the catalyst was prepared in situ using $[Ir(cod)Cl]_2$, **L***, and dry TBD. [b] Isolated yield of branched product **2**. [c] Determined by ^1H NMR of the crude product. [d] Determined by HPLC. [e] Reaction was carried out at 50 °C.

The pronucleophile **Nu3** fulfills conditions (a)−(c) enumerated above. Likely, Weinreb type reactions[19] cannot be carried out with hydroxamates derived from **Nu3**. Therefore, **Nu4**[20] was probed. This was found to be slightly less reactive than **Nu3**; therefore, reactions were run at 50 °C rather than at rt (Table 2). Regioselectivity was slightly lower with **Nu4** than with **Nu3** for reactions of substrates **1a**, **1c**, and **1d** (Table 1, entries 1, 3, 5 vs Table 2, entries 1, 6, 8). Enantioselectivities were excellent for the substrates **1a**−**d**.

Reactions catalyzed with the (π-allyl)Ir complex **C1** were particularly fast and proceeded with very high regio- and enantioselectivity with substrates **1a**−**c** (entries 3, 5, 7). For substrates **1d** and **1e**, typically,[21] lower regioselectivity was obtained; in these cases improvement was possible with dbcot as an auxiliary ligand (entries 11, 15, 16). Further improvement was possible by replacement of TBD as a base, used for in situ activation or as an additive, by DBU[9c] (entries 2, 9) or 4-(dimethylamino)pyridine (DMAP) (entry 12). For substrate **1e** the best result was obtained with **C3** as the catalyst (entry 16).

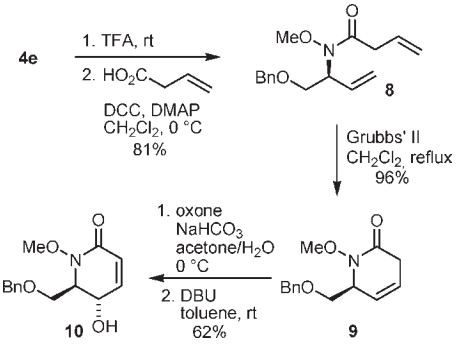
Table 2. Ir-Catalyzed Allylic Substitutions with the Pronucleophile **Nu4** [a]

entry	substrate	catalyst	base	time (h)	yield (%)[b]	b/l[c]	ee (%)[d]
1	**1a**	in situ/**L2**	TBD	24	58	94:6	94
2	**1a**	in situ/**L2**	DBU	2	92	97:3	99
3	**1a**	**C1**	TBD	1.5	59	96:4	98
4	**1b**	in situ/*ent*-**L2**	TBD	1	76	98:2	98
5	**1b**	*ent*-**C1**	TBD	1	75	99:1	98
6	**1c**	in situ/**L2**	TBD	2.5	74	90:10	98
7	**1c**	**C1**	TBD	1	80	93:7	99
8	**1d**	in situ/**L2**	TBD	5	80	87:13	97
9	**1d**	in situ/**L2**	DBU	4.5	88	87:13	98
10	**1d**	**C1**	TBD	2	83	88:12	98
11[e]	**1d**	in situ/**L2**	TBD	3	86	95:5	94
12[e]	**1d**	in situ/**L2**	DMAP	3	88	96:4	98
13	**1e**	in situ/*ent*-**L2**	DBU	2	47	71:29	86
14	**1e**	**C1**	DBU	1	63	78:22	91
15	**1e**	**C2**	DBU	1	71	90:10	88
16	**1e**	**C3**[f]	DBU	20	72	94:6	93

[a] All reactions were carried out at 50 °C. [b] Combined yield of **4** + **5**. [c] Determined by ^1H NMR of the crude product. [d] Determined by HPLC or GC. [e] $[Ir(dbcot)Cl]_2$ was used instead of $[Ir(cod)Cl]_2$. [f] 2.7 mol % of the catalyst were used. The yield refers to pure **4e**.

As an application of the hydroxamates, the sequence described in Scheme 3 was carried out. Removal of the Boc protecting group with TFA followed by acylation with vinylacetic acid furnished the diene **8** (81%), which was subjected to ring closing metathesis (RCM) to give the piperidone **9** in 96% yield. Finally, an approach toward aza-sugars, a catch and release strategy,[22] was employed by epoxidation and base-catalyzed elimination to give compound **10**. The epoxidation, using a procedure of Knight,[22b,c] proceeded with a diastereoselectivity of 95:5.[23]

Scheme 3. Short Approach toward Aza-Sugars



After the promising results presented in Scheme 3, a shorter route using pronucleophile **Nu5** was investigated (Scheme 4). It was anticipated that the substitution products, e.g., **11**, derived from **Nu5** could be directly cyclized

(15) For preparation, see: (a) Spiess, S.; Raskatov, J. A.; Gnamm, C.; Brödner, K.; Helmchen, G. *Chem.—Eur. J.* **2009**, *15*, 11087–11090. (b) Raskatov, J. A.; Spiess, S.; Gnamm, C.; Brödner, K.; Rominger, F.; Helmchen, G. *Chem.—Eur. J.* **2010**, *16*, 6601–6615. (c) Madrahimov, S. T.; Markovic, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *133*, 7228–7229. (d) Gärtner, M.; Mader, S.; Seehafer, K.; Helmchen, G. *J. Am. Chem. Soc.* **2011**, *133*, 2072–2075.

(16) The assignment of the relative configuration of **7** is tentative.

(17) (a) Le Flohic, A.; Meyer, C.; Cossy, J.; Desmurs, J.-R. *Tetrahedron Lett.* **2003**, *44*, 8577–8580. (b) Reddy, V. K.; Miyabe, H.; Yamauchi, M.; Takemoto, Y. *Tetrahedron* **2008**, *64*, 1040–1048.

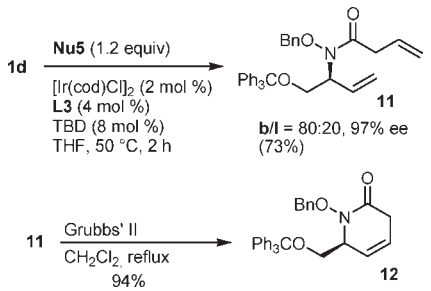
(18) (a) Bates, R. W.; Snell, R. H.; Winbrusch, S. *Synlett* **2008**, 1042–1044. (b) Bates, R. W.; Song, P. *Synthesis* **2009**, 655–659.

(19) Review: Balasubramaniam, S.; Aidhen, I. S. *Synthesis* **2008**, 3707–3738.

(20) Kawase, M.; Kitamura, T.; Kikugawa, Y. *J. Org. Chem.* **1989**, *54*, 3394–3403.

(21) (a) Gnamm, C.; Franck, G.; Miller, N.; Stork, T.; Brödner, K.; Helmchen, G. *Synthesis* **2008**, 3331–3350. (b) Lee, J. H.; Shin, S.; Kang, J.; Lee, S. *J. Org. Chem.* **2007**, *72*, 7443–7446.

Scheme 4. Ir-Catalyzed Allylic Amination with **Nu5** Followed by Ring Closing Metathesis



by RCM to give piperidines of interest in the synthesis of biologically active compounds. On the other hand, **Nu5** and the allylation product are prone to suffer base-catalyzed rearrangement to the corresponding crotonamides.

(22) (a) Franck, G.; Brödner, K.; Helmchen, G. *Org. Lett.* **2010**, *12*, 3886–3889. (b) Knight, J. G.; Tchabanenko, K. *Tetrahedron* **2003**, *59*, 281–286. (c) Robertson, J.; Abdulmalek, E. *Tetrahedron Lett.* **2009**, *50*, 3516–3518.

(23) The feasibility of Weinreb type chemistry was checked with amide **8**. Upon addition of DIBAL-H at −78 °C the deacylation product, *N*-{(1*S*)-1-[(benzyloxy)methyl]prop-2-en-1-yl}-*O*-methylhydroxylamine (**4e′**), was isolated in 96% yield.

(24) Rajendra, G.; Miller, M. J. *Tetrahedron Lett.* **1985**, *26*, 5385–5388.

Nu5 was readily prepared according to a modified procedure of Rajendra and Miller.[24] Allylic amination of **1d** with **Nu5** (Scheme 4) under salt-free conditions proceeded with excellent enantioselectivity albeit with a somewhat low degree of regioselectivity. Ring closing metathesis of **11** proceeded smoothly to give the piperidone **12** with the same substitution pattern as that for **9**.

In conclusion, we have found that asymmetric Ir-catalyzed allylic aminations with hydroxamic acid derivatives can be carried out with excellent regio- and enantioselectivities. Hydroxamic acids derived from vinylacetic acid yield products that can be directly subjected to RCM to yield piperidines suitable for transformation into azasugars and alkaloids.

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Supporting Information Available. Experimental procedures, characterization of compounds, determination of regio- and enantioselectivities. This material is available free of charge via the Internet at http://pubs.acs.org.