Synthetic Methods

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Thiol-Catalyzed Stereoselective Transfer Hydroamination of Olefins with N-Aminated Dihydropyridines**

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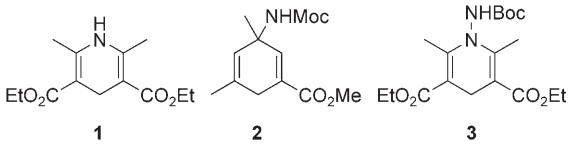
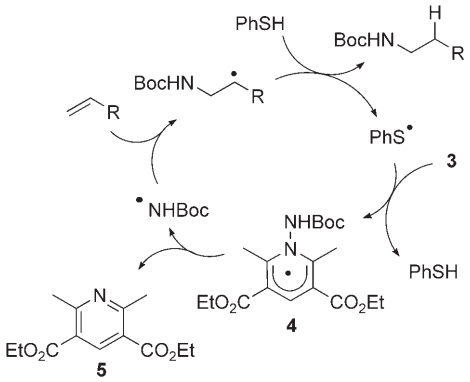
The Hantzsch dihydropyridine **1** has recently been used as a transfer-hydrogenation reagent in the organocatalytic reduction of imines,[1] α,β-unsaturated aldehydes,[2] and pyridines.[3] These reductions proceed by hydride transfer from the dihydropyridine to an activated acceptor. However, the application of Hantzsch-type dihydropyridines as H donors in radical chain reactions has not been reported to date. We have recently shown that the aminated cyclohexadiene **2** (Moc = methyloxycarbonyl) is an efficient reagent for transition-metal-free radical-transfer hydroamination of various olefins.[4] The doubly activated methylene group in **2** acts as an H donor. Drawbacks of our reagent **2** are: 1) Large-scale synthesis of **2** is rather tedious, 2) compound **2** readily decomposes under acidic conditions, and 3) stereoselective hydroaminations are highly unlikely since reactions with **2** have to be conducted at 140 °C.



Transition-metal-mediated hydroaminations of olefins have been intensively investigated. However, these methods lack generality and therefore novel procedures are still highly desirable.[5] Herein we introduce the N-aminated Hantzsch ester **3** (Boc = *tert*-butyloxycarbonyl) as a readily available nontoxic[6] radical-transfer-hydroamination reagent. Moreover, we will present stereoselective hydroaminations of chiral enecarbamates for the preparation of vicinal diamines. Since these compounds are biologically interesting, the synthesis of chiral 1,2-diamines has recently received increasing attention.[7]

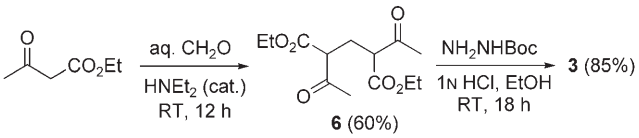
Hydrogen transfers from carbon atoms to carbon radicals are generally inefficient processes. Therefore, we planned to apply polarity-reversal catalysis (PRC).[8] We believed that PhSH would be a good catalyst for our chain reaction, since it efficiently reduces C-centered radicals to give the corresponding thiyl radicals, which should be reduced by reagent **3** (polarity match) to reform the thiol catalyst (Scheme 1). The



Scheme 1. Radical transfer hydroamination with **3** using polarity-reversal catalysis (PRC).

radical **4** thus formed should readily aromatize to generate the carbamoyl radical (•NHBoc) and pyridine **5**.[9] The driving force of the overall reaction is the aromatization yielding **5**. In addition, the weak N–N bond in **4** should further support the elimination. Addition of the N radical to the acceptor RCH=CH_2 would lead to the corresponding β-amidyl alkyl radical, which would be eventually reduced with PhSH to propagate the chain reaction.

Reagent **3** was readily prepared on a large scale in two steps (Scheme 2). Reaction of ethyl acetylacetate with



Scheme 2. Synthesis of hydroamination reagent **3**.

formaldehyde afforded the diester **6**, which underwent condensation with Boc-protected hydrazine to give **3** in good yield.[10]

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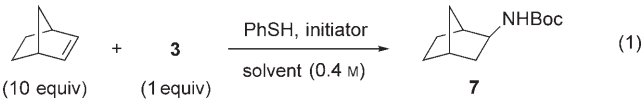
Radical hydroamination was first studied with norbornene as the acceptor [Eq. (1)]. Reaction of norbornene (10 equiv) with **3** (1 equiv) in refluxing benzene under typical radical conditions (0.3 equiv α,α′-azobisisobutyronitrile, AIBN) in the presence of PhSH (0.15 equiv) afforded **7** in 54% yield (Table 1, entry 1). Importantly, pyridine **5**, which

Table 1: Hydroamination of norbornene with **3** under different conditions.



(1)

Entry	Solv.	*T* [°C]	PhSH [equiv]	Init.[a]	Yield [%][b]
1	C_6H_6	80	0.15	AIBN	54
2	C_6H_6	20	0.15	air	57
3	C_6H_6	20	0.15	Et_3B/O_2[c]	60
4	C_6H_6	0	0.15	Et_3B/O_2[c]	51
5	$C_6H_5CH_3$	20	0.15	Et_3B/O_2[c]	42
6	CH_2Cl_2	20	0.15	Et_3B/O_2[c]	46
7	$ClCH_2CH_2Cl$	20	0.15	Et_3B/O_2[c]	54
8	$ClCH_2CH_2Cl$	−30	0.15	Et_3B/O_2[c]	53
9	CH_2Cl_2	−80	0.15	Et_3B/O_2[c]	46
10	C_6H_6	20	–	AIBN	40
11	C_6H_6	20	0.20	Et_3B/O_2[c]	56
12	C_6H_6	20	0.10	Et_3B/O_2[c]	51
13	C_6H_6	20	0.05	Et_3B/O_2[c]	44

[a] Initiator: 0.1 equiv of Et_3B or 0.3 equiv of AIBN were used. [b] Yields of isolated products. [c] Air was used as O_2 source.

was obtained as a side product, was readily separated. Hydroamination at room temperature with Et_3B/O_2 as the initiator (0.1 equiv) afforded **7** in 60% yield (Table 1, entry 3), and similar results were obtained in the absence of Et_3B with only air as the initiator (Table 1, entry 2). Hydroamination in benzene was also conducted at 0°C without affecting the yield to a large extent (Table 1, entry 4). With toluene or CH_2Cl_2 as solvents slightly lower yields were obtained (Table 1, entries 5 and 6). Dichloroethane was tolerated as the solvent at both room temperature (Table 1, entry 7) and at −30°C (Table 1, entry 8). Hydroamination still occurred even at −80°C in CH_2Cl_2 (Table 1, entry 9). A lower yield was obtained in the absence of thiol catalyst, supporting our assumption that the reduction of a C radical with **3** is a rather inefficient process (Table 1, entry 10). Increasing the amount of thiol to 0.2 equiv did not provide better results (compare Table 1, entries 3 and 11), and with 0.1 equiv of PhSH the reaction was still efficient (Table 1, entry 12). However, lowering the catalyst loading to 0.05 equiv led to a slightly diminished yield (Table 1, entry 13). Therefore, all the following experiments were conducted with 0.10–0.15 equiv of PhSH.

To document the scope of our method, various olefins were reacted with **3** (Figure 1). These hydroaminations were conducted in benzene either at room temperature with Et_3B/O_2 (method A) or at 80°C with AIBN as initiators (method B) for 10 to 12 h. Reaction with 1-octene delivered **8** in 44% yield as well as the regioisomeric Markovnikov product (not shown) in 6% yield. For all other substrates tested,

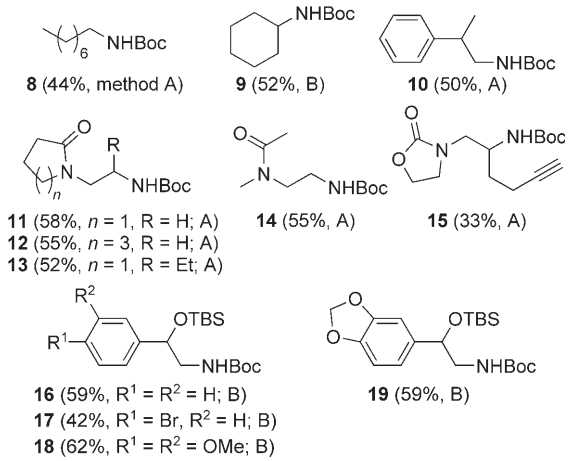
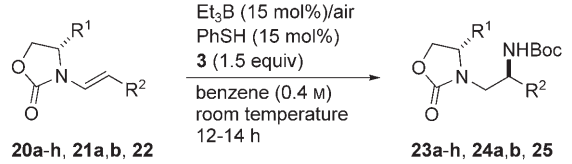


Figure 1. Hydroamination of various olefins. Reaction conditions: benzene (0.4 M), olefin (2–10 equiv), reagent **3** (1 equiv). TBS = *tert*-butyldimethylsilyl.

hydroamination occurred highly regioselectively to give the anti-Markovnikov product only. Hydroamination of cyclohexene gave **9** in 52% yield. A similar yield was obtained for the reaction of β-methylstyrene (→**10**, 50%). Electron-rich vinyl amides were good acceptors for the radical hydroamination (→**11**–**14**). With the enecarbamate bearing an alkynyl substituent we achieved a slightly lower yield (→**15**). The biologically interesting protected 1,2-amino alcohols **16**–**19** were isolated in moderate to good yields (42–62%). In contrast to metal-catalyzed aminations where Markovnikov products have been obtained,[5] our method delivered anti-Markovnikov compounds. Hence, our hydroamination nicely complements existing metal-mediated reactions. Moreover, our method directly delivered protected amines, which were readily isolated.

Importantly, as hydroaminations can be conducted at low temperatures with reagent **3**, stereoselective intermolecular radical hydroaminations could be studied, which to the best of our knowledge have not been reported to date. We selected enecarbamates derived from Evans oxazolidinones[11] as chiral acceptors (Scheme 3). Chiral enecarbamates have



Scheme 3. Stereoselective radical transfer hydroaminations. R^1 and R^2 are specified in Table 2; only the major isomer of the product is shown.

been used successfully in stereoselective cycloadditions;[12,13] however, stereoselective radical reactions using chiral enecarbamates were unprecedented.[14,15] The chiral *E*-enecarbamates **20a–h**, **21a,b**, and **22** were readily prepared by condensation of an Evans oxazolidinone with the corresponding aldehyde.[16]

Hydroaminations were conducted in benzene at room temperature to give the corresponding protected vicinal diamines **23a–h**, **24a,b**, and **25**. Good selectivities were obtained for the hydroamination of **20a** and **20b** (Table 2,

Table 2: Hydroamination of chiral enecarbamates.

Entry	Olefin	R^1	R^2	Yield [%] (product)	d.r.
1	**20a**	*i*Pr	Et	47 (**23a**)	13:1[a]
2	**20b**	*i*Pr	Bu	48 (**23b**)	13:1[a]
3	**20c**	*i*Pr	*i*Pr	33 (**23c**)	13:1[a]
4	**20d**	*i*Pr	*t*Bu	30 (**23d**)	20:1[a]
5	**20e**	*i*Pr	PMB[c]	40 (**23e**)	13:1[b]
6	**20f**	*i*Pr	$(CH_2)_3Ph$	44 (**23f**)	13:1[b]
7	**20g**	*i*Pr	$(CH_2)_3CO_2Et$	41 (**23g**)	13:1[b]
8	**20h**	*i*Pr	$(CH_2)_2OAc$	48 (**23h**)	13:1[b]
9	*ent*-**21a**	Ph	Et	48 (*ent*-**24a**)	11:1[b]
10	*ent*-**21b**	Ph	*i*Pr	34 (*ent*-**24b**)	11:1[b]
11	**22**	*t*Bu	Et	48 (**25**)	14:1[a]

[a] Diastereomeric ratio (d.r.) determined by gas chromatography. [b] d.r. determined by ^{1}H NMR spectroscopy. [c] PMB = *para*-methoxybenzyl.

entries 1 and 2). Increasing the size of the R^2 substituent from a primary alkyl group to an isopropyl group led to a decrease of the yield without affecting the selectivity (Table 2, entry 3). However, the stereoselectivity significantly increased for the *tert*-butyl-substituted carbamate **20d** (entry 4). Functional groups in the side chain did not affect the selectivity (Table 2, entries 5–8). As expected, the size of the stereodirecting R^1 substituent influenced the selectivity. Slightly worse results were obtained for the Ph-substituted enecarbamates *ent*-**21a,b** (Table 2, compare entries 1 and 3 with 9 and 10), whereas the *t*Bu derivative **22** provided a higher selectivity (Table 2, entry 11).

The relative configuration was assigned unambiguously by X-ray analysis of the major isomer of product **23c** (Figure 2).

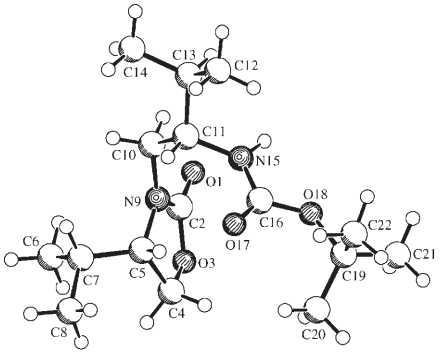


Figure 2. Molecular structure of the major isomer of the protected 1,2-diamine **23c**.

The configuration of all other products was assigned in analogy. The stereoselectivity can be explained by the model depicted in Figure 3. The carbamoyl radical approaches the olefin from the side opposite to the shielding R^1 substituent. The enecarbamate reacts via its most stable conformer **B**. The

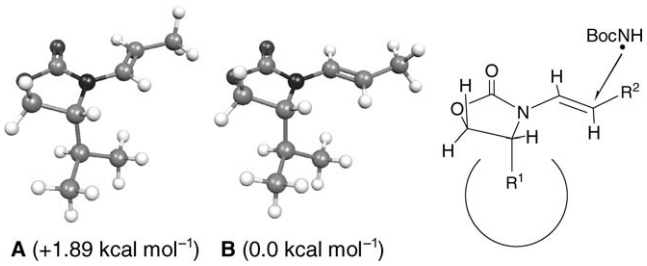


Figure 3. Conformers **A** and **B** of *ent*-**20i** and model to explain the stereoselectivity. The energy difference mainly results from dipole interactions of the C=O and C=C bonds.

energy difference between the two conformers **A** (+1.89 kcal mol^{-1}) and **B** was calculated for compound **20i** (R^1 = *i*Pr, R^2 = Me) by using density functional theory (DFT, B97-D/TZVP).[13]

In conclusion, we introduced the N-aminated dihydropyridine **3** as a novel precursor for the generation of carbamoyl radicals. Compound **3** was prepared in two steps using readily available starting materials. Radical anti-Markovnikov hydroaminations on various olefins were performed. Moreover, protected vicinal diamines were prepared with good selectivities by hydroamination of chiral enecarbamates.

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