ORGANIC LETTERS

2010
Vol. 12, No. 16
3690−3692

Acyclic Stereocontrol in the Catalytic C−H Amination of Benzylic Methylene Groups

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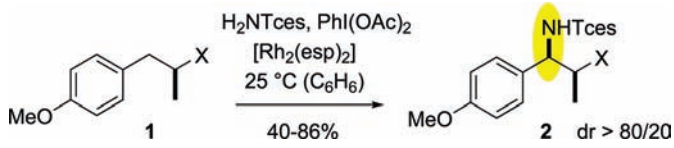
Received July 2, 2010

ABSTRACT



Diastereotopos-differentiation is the key feature of the catalytic C−H amination at the benzylic position of substrate 1. Essentially independent of the functional group X (X = COOMe, $PO(OEt)_2$, SO_2Ph, NO_2, CN, OAc), the depicted products 2 are formed with good (dr = 80/20) to excellent (dr > 95/5) diastereoselectivity. The reaction proceeds without racemization and possesses potential for the C−H amination of open-chain substrates.

The direct catalytic amination of alkanes is one of the most important methods for aliphatic C−H bond functionalization.[1] In this process, an appropriate nitrene precursor is often employed in the presence of a suitable metal catalyst to generate a reactive metal nitrene complex, which then undergoes C−H insertion according to an "outer sphere" mechanism.[2] Rhodium is the most important metal for the amination, and a wide range of rhodium catalysts can be applied to this transformation.[3] To the best of our knowledge, there have yet been no studies regarding the stereochemical outcome of this reaction in the case that a methylene group of an acyclic substrate is attacked intermolecularly[4] under C−H amination conditions.

Our interest in this transformation stems from the fact that we have recently observed a significant differentiation of the two diastereotopic faces in the reactions of chiral cations of type **1** (Figure 1).[5] Hence, we wondered whether a differentiation[6] of the diastereotopic hydrogen atoms in substrates of type **2** could also be possible and what preference

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10.1021/ol101517v
Published on Web 07/22/2010

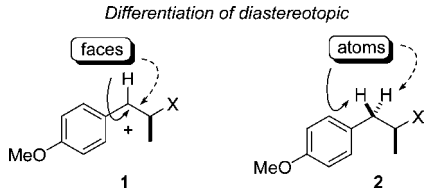
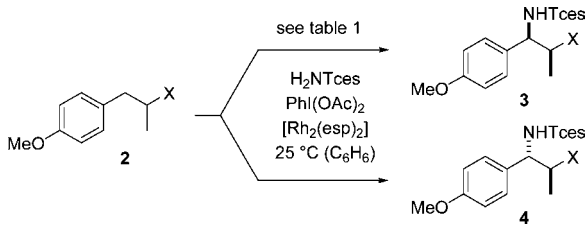


Figure 1. Diastereoselective reactions at the prostereogenic carbon atom in cations of type **1** and in hydrocarbons of type **2**.

would be observed. Herein, we report on our preliminary results in this area.

Our first experiments were aimed at identifying an appropriate nitrene precursor and a sufficiently active catalyst. It was found for our test substrates that the combination of a trichloroethoxysulfonyl-substituted amine (H_2NTces) with bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionate)] [$Rh_2(esp)_2$] as the catalyst and diacetoxyiodobenzene as the oxidant, as previously described by Du Bois,[3d,g] was superior to other published reagent combinations. Various chiral substrates of type **2** reacted under the conditions that are outlined in Scheme 1 and described in detail in the Supporting Information.

Scheme 1. C−H Amination of Substrate **2** to the Diastereomeric Products **3** and **4**



Remarkably, the reactions proceeded with good to excellent diastereoselectivity with a range of substituents (X) on the stereogenic center adjacent to the benzylic methylene group (Table 1). Most noteworthy is the fact that, in contrast to the reactions of cations of type **1**, the size of the substituent (X) has a negligible effect on the direction of the selectivity. Although, the best selectivities were obtained with the formally biggest groups $PO(OEt)_2$ (entry 2) and SO_2Ph (entry 3), other groups that are according to their A-value[7] significantly smaller than the methyl substituent, for example, COOMe (entry 1), NO_2 (entry 4), CN (entry 5), or OAc

Table 1. Diastereotopos-Differentiation in C−H Amination Reactions at the Benzylic Position of Chiral Substrates **2**

entry[a]	substrate	X	yield [%][b]	dr[c]
1	**2a**	COOMe	81	82/18
2	**2b**	$PO(OEt)_2$	65	>95/5
3	**2c**	SO_2Ph	56	>95/5
4	**2d**	NO_2	63	91/9
5	**2e**	CN	86	80/20
6	**2f**	OAc	40[d]	86/14

[a] H_2NTces (0.5 mmol) and $Rh_2(esp)_2$ (0.01 mmol) were dissolved in benzene (1.5 mL). Substrate **2** (1.0 mmol) was added to the stirred solution at 25 °C, and the oxidant (0.75 mmol) was added in portions over 2 h. The reaction was quenched with a saturated aqueous solution of thiourea after 16 h. [b] Yields of the diastereomeric mixture based on nitrene source H_2NTces. [c] The diastereomeric ratio (dr = **3**/**4**) was determined by ^{1}H NMR. [d] Incomplete conversion; impure H_2NTces was reisolated.

(entry 6), also afforded the major diastereomer **3** with good selectivity. A reversal of the selectivity in favor of diastereomer **4** was not observed in any case. To secure high conversion of the reactive nitrene precusor, H_2NTces was used as the limiting reagent. In most cases (entries 1−5) it was not reisolated. If a 1:1 ratio of H_2NTces and substrate **2** was used, the yields were lower. For example substrate **2b** gave a 45% yield for a ratio H_2NTces:**2b** = 1:1 and a 60% yield if the ratio was 1:1.5.

The relative configuration of the major diastereomers **3a**, **3b**, **3c**, **3d**, and **3f** was determined by X-ray crystal structure analysis. As an example, the relative configuration of product **3a** is depicted in Figure 2. In this case, the structure could be

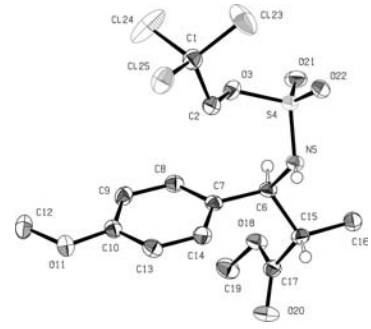


Figure 2. Proof of relative configuration of the product **3a** by crystal structure analysis.

confirmed following cleavage of the protecting group (Zn/Cu in MeOH/HOAc, then AcCl in MeOH) by comparing the ^{1}H NMR spectra of the deprotected amine with the literature data.[8] The relative configuration of the acetate **3f** was confirmed in the same manner.[9] Using the Pinner reaction,[10] nitrile **3e** was transformed into methyl ester **3a**, the configuration of which was known from its crystal structure.

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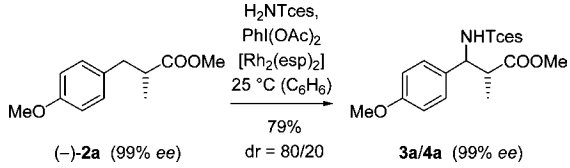
In the case of substrate **2f**, we attempted to improve the yield by substituting the acetyl group with different oxygen protecting groups. Although the selectivities increased, the yields were lower. As an example, the corresponding benzoate was obtained with a selectivity of dr = 95/5, but in only 24% yield. Interestingly, the compound, which is homologous to **2f**, bearing a CH_2OAc group (X = CH_2OAc) on the stereogenic center exhibited significantly lower selectivity (dr = 60/40) but a higher yield (70%).

Enantiomerically pure substrate (−)-**2a**, which was obtained by an auxiliary-controlled alkylation,[11] was employed to prove that the C−H amination did not lead to racemization (Scheme 2). The reaction proceeded in complete analogy to

Scheme 2. Proof of Configurational Stability in the C−H Amination of Ester (−)-**2a**



the reaction of racemate **2a**. Both diastereomeric products **3a** and **4a** possessed, according to HPLC analysis, the same enantiomeric excess (>99% ee) as the starting material.

On the basis of the mechanistic experiments of Du Bois et al. with H_2NTces, $PhI(OPiv)_2$ and $Rh_2(esp)_2$[3g,12] it can be assumed that the reaction is concerted and proceeds via a singlet nitrene complex. The reaction takes place at the most nucleophilic C−H bond because the intermediate nitrene complex is electrophilic.[4a,13] Assuming a staggered conformation to be preferred for compounds **2**, the two conformations **2′** and **2″** should be predominantly responsible for the reaction outcome (Figure 3). The marked C−H bond, which

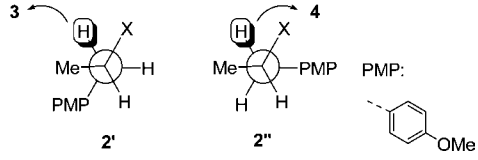


Figure 3. Conformations **2′** and **2″** of the substrate **2** in the studied diastereoselective C−H amination.

is positioned antiperiplanar to the C−H bond at the stereogenic center, should exhibit electron density higher than that of the synclinal C−H bond and should be more reactive. The C−H amination of the starting material in conformation **2′** gives the major product **3**, and the rotamer **2″** is responsible for the formation of the corresponding byproduct **4**. A preference for rotamer **2′** over rotamer **2″** may be the result of dipole minimization with the substituents X and *p*-methoxyphenyl being oriented in an antiperiplanar fashion. Although preliminary DFT calculations support this hypothesis, additional work is required to further elucidate the selecitivity parameters.

In a final set of experiments, which have yet to be optimized, we tested whether the scope of the substrates could be increased by variation of the oxidant. In a recent report it was indicated that the use of $PhI(OOCCMe_2Ph)_2$ could significantly improve the catalytic performance of $Rh_2(esp)_2$ in intermolecular C−H amination reactions, because the respective carboxylic acid is more effective than HOAc or HOPiv in reducing $[Rh_2(esp)_2]^+$.[14]

Indeed, the less reactive substrates **5a** and **5b**, which gave very low yields with $PhI(OAc)_2$ or $PhI(OPiv)_2$ as the oxidant, could be converted into the respective products in 43% and 50% yield when $PhI(OOCCMe_2Ph)_2$ was used as the oxidant. As in the previous example (Table 1, entry 6), in which a moderate yield was recorded, the substrates **5a** and **5b** as well as the nitrene precursor H_2NTces were reisolated. It appears as if the less than perfect yields stem from unwanted oxidant decomposition rather than from any unselective reactions of the substrates **2f** and **5**.

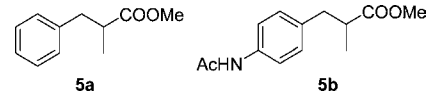


Figure 4. Structure of less reactive substrates **5a** and **5b**.

In summary, the C−H amination of arylalkanes possessing a stereogenic center at the β-position occurs at the α-position with amazingly high diastereoselectivity. The reaction proceeds without racemization of a stereogenic center in the β-position and is therefore suitable for the preparation of functionalized amines in the context of acyclic stereocontrol. The elucidation of the exact course of the reaction and the substantiation of the diastereotopos-differentiation require further investigations, which are currently in progress.

Acknowledgment. This project was supported by an Alexander von Humboldt postdoctoral research fellowship to P.H. and by the Deutsche Forschungsgemeinschaft (Ba 1372-12).

Supporting Information Available: Representative experimental procedures and spectral data for all new compounds; crystallographic data (CIF format) for compounds **3a**, **3b**, **3c**, **3d**, and **3f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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