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Kinetic Diastereomer Differentiation in Au(III)- and Bi(III)-Catalyzed Benzylic Arylation: Concise and Stereocontrolled Synthesis of 2-Amino-1,1-diarylalkanes

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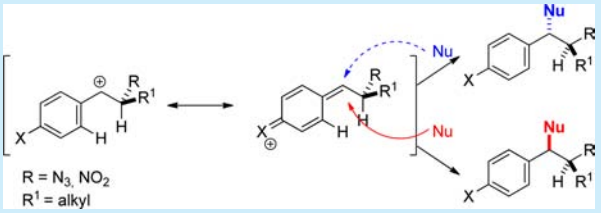
Supporting Information

ABSTRACT: Benzylic alcohols carrying an adjacent α-nitro or α-azido group on the alkane chain are converted into *syn*-1,1-diaryl-2-nitro- and 2-azidoalkanes with electron-rich arenes in stereoselective reactions catalyzed by Brønsted and Lewis acids. Gold(III) chloride and bismuth(III) triflate were found to be especially efficient as catalysts, showing kinetically controlled differentiation in the reactivity of diastereomeric α-substituted benzyl alcohols. Applications to therapeutically relevant *syn*- and *anti*- 2-amino-1,1-diarylalkanes are projected.



The phenylethylamine moiety is a well-known pharmacophoric unit in a number of CNS-active drugs, varying in their biological activities and structural complexity, as exemplified by amphetamine, the simplest of potent stimulants, to morphine, the most powerful analgesic.[1] The inclusion of an arene moiety at the benzylic position of a phenylethylamine core unit generates a new family of 2-amino-1,1-diarylalkanes with equally important biological functions in the CNS and cardiovascular areas (Figure 1).[2]

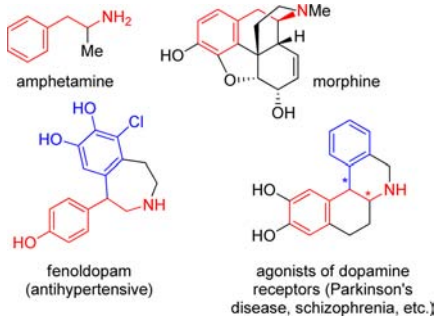


Figure 1. Phenylethylamine core in selected CNS-active compounds.

Despite their apparent structural simplicity, stereocontrolled access to 2-amino-1,1-diarylalkanes remains a challenge.[3] One approach involves the generation of a benzylic carbocation and the introduction of an arene moiety in an S_N1-like process. Indeed, scholarly reports by Bach,[4a−d] Prakash,[4b,d] and Olah[4b,d] have shown that highly diastereoselective introduction of electron-rich arenes and some heteroarenes as nucleophiles can be achieved under Brønsted acid catalysis even at −78 °C. The stereoselectivity has been rationalized on the basis of resonance stabilized benzylic carbenium ions, bearing a substituent on the adjacent α-stereocenter, in which bond rotation is minimized due to 1,3-allylic strain, thus allowing differentiation of the nucleophile approach on the planar C(sp^2) carbocation (Figure 2).[4]

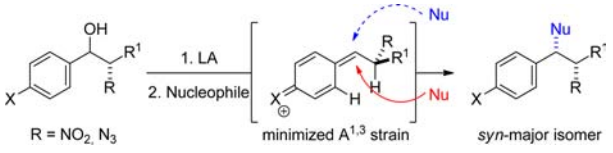


Figure 2. Mechanistic rationale for diastereoselectivity.

These seminal findings were exploited in the first Au(III)-catalyzed benzylation of arenes by Beller et al.,[5] leading to 1,1-diarylalkanes in high yields and chemoselectivities. Concurrently, Bach et al.[6] reported highly diastereoselective Friedel−Crafts arylations of α-functionalized benzylic carbocations to give *syn*- and *anti*- adducts depending on the nature of the resident functional group on the alkane chain. A single example of a nitro substituent showed excellent *syn*-selectivity with 1,3-dimethoxybenzene as the nucleophile utilizing 10 mol % $AuCl_3$ in nitromethane as solvent.[4e,6] *Anti*-selectivity has been observed in the Friedel−Crafts alkylation of α-aryl benzylic cations with indoles as nucleophile catalyzed by TFA or BF_3·Et_2O.[7]

Herein we report on the stereocontrolled arylations of a series of α-nitro and α-azido benzylic alcohols as a concise method to access a variety of 2-amino-1,1-diarylalkanes.[8] It was anticipated that the use of a Brønsted or Lewis acid would lead to the formation of a quinonoid oxocarbenium ion intermediate, which would be attacked at the benzylic position to generate the corresponding diastereomeric products.[4] Using

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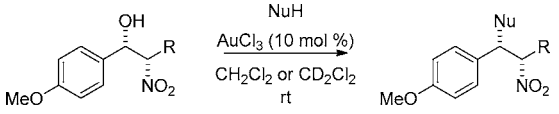
the (±)-nitroalcohol derivative **1** as a model with 1,3-dimethoxybenzene as an arene nucleophile in the presence of a series of catalysts led to the *syn*-diastereomer **2** in good to excellent yields.[9]

Based on preliminary observations, it was decided $AuCl_3$[5,6,11] and $Bi(OTf)_3$[12] would be used as catalysts in this series, with a variety of aromatic and heteroaromatic nucleophiles. Excellent diastereoselectivities favoring the *syn*-orientation and in preparatively useful yields were obtained in general as shown in Table 1.

Table 1. Scope of 2-Nitro-1,1-Diarylalkanes[a]



1 R = Et 2-11

entry	R	NuH	product	time	yield, dr
1	Et	1,3-dimethoxybenzene	**2**	29 h	91%,[b] >20:1
2	Et	1-methoxynaphthalene	**3**	40 h	83%[c], 8:1[d]
3	Et	anisole	**4**	72 h	94%
4	Et	1,2,3-trimethoxybenzene	**5**	24 h	90%, >20:1
5	Et	2-methylfuran	**6**	16 h	78%, 19:1
6	Et	3,5-dimethoxystyrene	**7**	24 h	85%,[e] >20:1
7	H	1,3-dimethoxybenzene	**8**	48 h	>95%
8	Allyl	1,3-dimethoxybenzene	**9**	16 h	66%,[f] >20:1
9	*n*Pr	1,3-dimethoxybenzene	**10**	2 h	80%, >20:1[g]
10	*n*Pr	2-methylfuran	**11**	4 h	60%, >20:1[g]

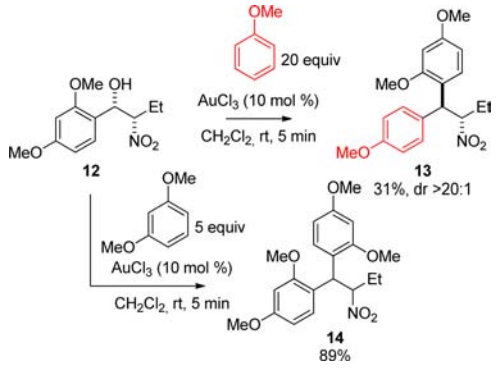
[a]Ratios were determined by ^{1}H NMR analysis of the crude materials, and yields were obtained after purification. [b]Full conversion was achieved within 30 min with 10 mol % of $Bi(OTf)_3$ in $MeNO_2$.[9] [c]Over 95% of the starting material **1** was consumed within 45 min, to give **3** with 10 mol % of $Bi(OTf)_3$ in $MeNO_2$.[9,10] [d]SFC separation and ^{1}H NMR of the pure sample of **3** gave a ratio of 9:1. [e]The crude ^{1}H NMR spectrum showed a 9:1 ratio of the regioisomers.[9] [f]Full conversion was achieved within 2 h, and a 92% yield of **9** was obtained with 10 mol % of $Bi(OTf)_3$ in $MeNO_2$.[9] [g]dr was calculated after purification.

The relative stereochemistry of the *syn*-diastereomers was determined by X-ray crystallographic analysis of **3**, which concurs with literature precedents and the general mechanistic rationale shown in Figure 2.[4a−e] Reaction times varied with the nature of the arene nucleophile, position of the methoxy group in the benzylic alcohol reacting partner, catalyst, and solvent.[13] A solvent scan revealed that dichloromethane and nitromethane were excellent, while toluene and diethyl ether resulted in lower conversion and the formation of byproducts.

The *anti*-isomer **13** can be obtained simply by starting with the nitroalcohol **12** and using anisole as the nucleophile. The reaction was completed within 5 min to give **13** as the major isomer, albeit in modest yield due to the comparatively weaker nucleophilicity of anisole (Scheme 1).[13] As expected, excellent conversion to **14** was observed when the more nucleophilic 1,3-dimethoxybenzene was used, highlighting the mutually cooperative effects of the reacting partners.[14]

In the course of our studies, we observed a preferential kinetic reactivity of the *syn*-nitroalcohols over the *anti*-isomers. Thus, when *syn*-*o*-methoxybenzyl nitroalcohol **15a** was used, the *syn*-1,1-diaryl product **16** was obtained as the major isomer

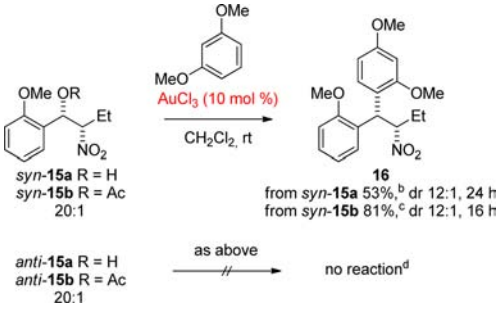
Scheme 1. Synthesis of the *anti*-Diastereomer 13[a]



[a]Ratios were determined by ^{1}H NMR analysis of the crude materials, and yields were obtained after purification.

within 24 h. In contrast, the *anti*-diastereomer of **15a** was recovered unchanged after 24 h (Scheme 2).

Scheme 2. Reactivity of Diastereomers[a]



[a]Ratios were determined by ^{1}H NMR analysis of the crude materials, and yields were obtained after purification. [b]From TLC analysis, the reaction did not achieve full conversion over a period of 24 h. [c]Full conversion within 16 h by TLC analysis. [d]No conversion was observed by TLC analysis, after 24 h.

This trend was also observed with the *p*-methoxybenzyl nitroalcohol **1**, in the presence of 1,3-dimethoxybenzene, 1-methoxynaphthalene, and 1,2,3-trimethoxybenzene as the arene nucleophile.[9] Monitoring the reaction of a 3:1 *syn*/*anti* mixture of **1** by ^{1}H NMR revealed virtual consumption of the *syn*-diastereomer within 60 min, while the *anti*-diastereomer required an additional 28 h to be almost fully consumed (Figure 3A), giving the same *syn*-adduct **2** as the major isomer (>20:1). Keeping $AuCl_3$ as the catalyst and using nitromethane as the solvent, the reaction was almost completed after only 2 h (Figure 3B). Faster conversion was observed when $Bi(OTf)_3$ was used as the catalyst in nitromethane (Figure 3C).[9]

The kinetically controlled selective reactivity of the *syn*-isomer **1**, with a $^3J_{Ha\text{-}Hb} \approx 9$ Hz,[15] can be rationalized based on a prevailing conformation favoring an antiperiplanar disposition of the alkyl group, and a gauche interaction between the nitro and hydroxy groups as illustrated in **A** (Figure 4). The $^3J_{Ha\text{-}Hb} \approx$ 5−6 Hz of the *anti*-isomer **B** suggests an average of more than one prevailing conformer in solution, such as $\mathbf{B_1}$, $\mathbf{B_2}$, and $\mathbf{B_3}$, hence a slower formation of the oxocarbenium ion.

The *syn*-isomers may benefit from a hyperconjugative donating effect in the antiperiplanar orientation in conformer **A**, which may also be a partial contributor in conformer $\mathbf{B_3}$ of the *anti*-isomer. The X-ray crystal structure of the methoxy-

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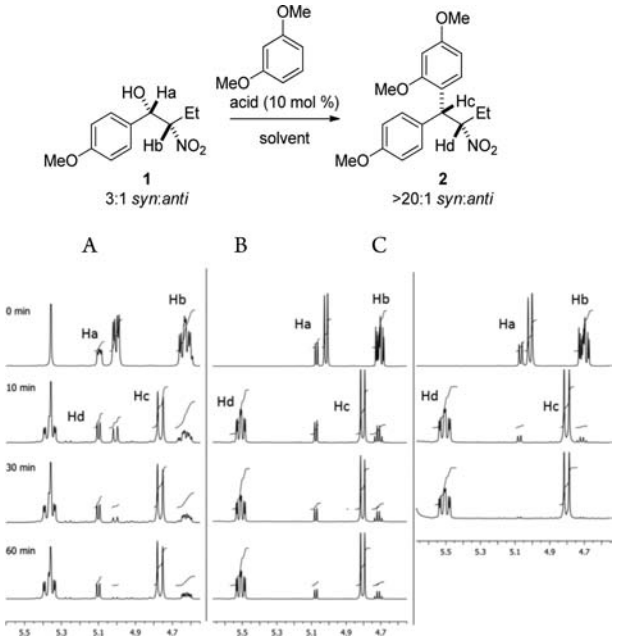


Figure 3. ^{1}H NMR time course for the *syn*- and *anti*-diastereomers of **1** as an initial 3:1 mixture: (A) using $AuCl_3$ in CD_2Cl_2; (B) using $AuCl_3$ in CD_3NO_2; (C) using $Bi(OTf)_3$ in CD_3NO_2.

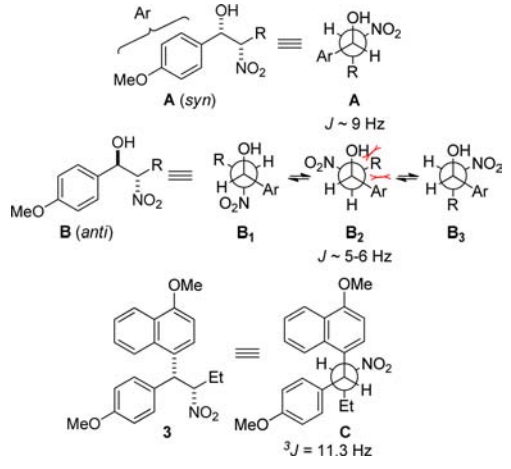
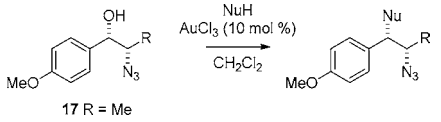


Figure 4. Possible conformers of *syn*- and *anti*-isomers (**A**, **B**).

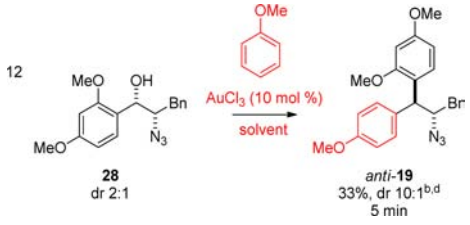
naphthyl analogue **3** conforms with projection **C**, in which C1 and C2 hydrogens are oriented in an antiperiplanar manner and steric effects are minimized compared to alternative conformations (Figure 4). This observation is also corroborated by the large coupling constant ($^3J_{Hc\text{-}Hd} \approx 11$ Hz) from ^{1}H NMR analysis.[4e,9]

Next, we explored different benzylic substitutions with α-azidoalkanes which are easily prepared either from the corresponding α-amino acids[16] in enantiopure form or via synthesis from cheap starting materials.[9] Using the same general protocol, a 2:1 *syn*/*anti* mixture of α-azidoalcohol **17** (*syn* $^3J_{Ha\text{-}Hb} = 7.6$ Hz; *anti* $^3J_{Ha\text{-}Hb} = 4.9$ Hz in $CDCl_3$) led to the *syn*-isomer **18** in excellent yield and good selectivity within 45 min (Table 2, entry 1). Compounds **19**−**23** were prepared in a similar manner (Table 2, entries 2−6). A solvent scan in this series also indicated a preference for dichloromethane and nitromethane while toluene and diethyl ether resulted in lower conversions. Interestingly, 1-methoxynaphthalene and 1-methylfuran proved to be poor nucleophiles in the case of the azido substrates. However, better yields and excellent *syn*-selectivity were still observed with 20 mol % of *p*-TsOH hydrate (Table 2, entries 7, 9, and 10).

Table 2. Synthesis of a Series of 2-Azido-1,1-diarylalkanes[a]



entry	R	NuH	product	time	yield, dr
1	Me	1,3-dimethoxybenzene	**18**	40 min	88%, 6:1[b]
2	Bn	1,3-dimethoxybenzene	**19**	20 min	88%, 7:1[b,c,d]
3	*i*Pr	1,3-dimethoxybenzene	**20**	40 min	82%, 6:1
4	*n*Pr	1,3-dimethoxybenzene	**21**	30 min	89%, 7:1
5	Me	anisole	**22**	30 min	64%[e]
6	Bn	1,2,3-trimethoxybenzene	**23**	40 min	81%, 16:1
7	Me	1-methoxynaphthalene	**24**	2 d	80%,[f] 5:1[g]
8	Me	1-methoxynaphthalene	**24**	16 h	14%[h]
9	Bn	1-methoxynaphthalene	**25**	24 h	55%, 6:1[g]
10	Bn	2-methylfuran	**26**	24 h	73%,[i] 5:1[g]
11	Me	*p*-toluenesulfonamide	**27**	3 d	70%, 5:1[j]



[a]Ratios were determined from ^{1}H NMR analysis of the crude materials, and yields were obtained after purification. [b]SFC separation of diastereomers was possible with **18** and **19**.[9] [c]See Supporting Information for results with $Bi(OTf)_3$ as the catalyst and $MeNO_2$ as the solvent. [d]Product was prepared from L-Phe.[9] [e]Diaryl **22** was obtained in 91% yield starting from the corresponding azidoacetate of **17**. [f]20 mol % of *p*-TsOH·H_2O was used as the catalyst since $AuCl_3$ or $Bi(OTf)_3$ resulted in a low yield. [g]Dr was calculated after purification. [h]55% of the starting material was recovered. [i]20 mol % of *p*-TsOH·H_2O was used, and the reaction was performed in $MeNO_2$. [j]Nu = $-NHSO_2C_6H_4Me$.

This approach was also successful with *p*-toluenesulfonamide as the nucleophile to generate a C−N bond (Table 2, entry 11). By reversing the aromatic moieties with 2,4-dimethoxyphenyl α-azidoalcohol (as in the nitro series, Scheme 2), the *anti*-isomer-**19** was obtained in a 33% yield with dr = 10:1 (Table 2, entry 12).

The *syn*-stereochemistry of the products in this series was confirmed by correlation with the α-nitro series by conversion to 2-amino-1,1-diarylpentane analogue **29** (Scheme 3).[9] Using $AuCl_3$ in CD_2Cl_2 the relatively faster reaction of the *syn*-diastereomer compared to the *anti*-isomer in the azido series was also observed by monitoring the reaction by ^{1}H NMR.[9]

In conclusion, we have developed stereocontrolled methods for the synthesis of a variety of 2-nitro and 2-azido 1,1-diarylalkanes using $AuCl_3$ and $Bi(OTf)_3$ as preferred catalysts. These should be immediate precursors to biologically relevant 2-amino-1,1-diarylalkanes.[17] An interesting kinetic differentiation was noticed between *syn*- and *anti*-α-nitro (and α-azido) benzylic alcohols during the $AuCl_3$ and $Bi(OTf)_3$ catalyzed arylation reactions. Further studies in benzylic functionalizations are in progress and will be reported in due course.

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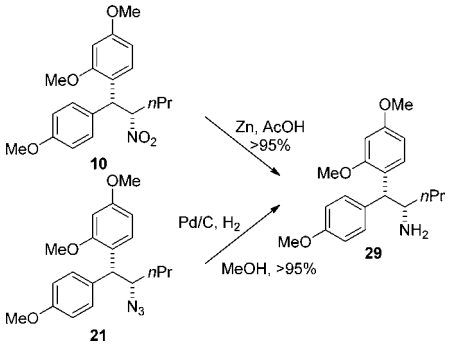
Scheme 3. Confirmation of the Relative Configuration



■ ASSOCIATED CONTENT

Supporting Information

Experimental details and analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(9) See Supporting Information.

(10) The corresponding *N*-acetyl product of **3** was also prepared. See **3Ac** in the Supporting Information.

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