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Synthetic Studies on Tricyclic Diterpenoids: Direct Allylic Amination Reaction of Isopimaric Acid Derivatives**

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A selective synthesis of 7- or 14-nitrogen containing tricyclic diterpenoids was completed according to a strategy in which the key step was the catalyzed direct allylic amination of methyl 14α-hydroxy-15,16-dihydroisopimarate with a wide variety of nitrogenated nucleophiles. It was revealed that the selectivity of the reaction depends on the nature of nucleophile. The catalyzed reaction of the mentioned diterpenoid allylic alcohol with 3-nitroaniline, 3-(trifluoromethyl)aniline, and 4-(trifluoromethyl)aniline yield the subsequent 7α-, 7β- and 14α-nitrogen-containing diterpenoids. The reaction with 2-nitroaniline, 4-nitro-2-chloroaniline, 4-methoxy-2-nitroaniline, phenylsulfamide, or *tert*-butyl carbamate proceeds with the formation of 7α-nitrogen-substituted diterpenoids as the main products.

Introduction

Isopimaric acid (**1**) (Figure 1) is a widely available tricyclic diterpenoid well represented in the resin of conifers of the genera *Pinus*, *Larix*, and *Picea*.[1] It exhibits interesting biological and pharmaceutical properties such as antimicrobial,[2] antiviral,[3] antiallergenic,[4] and anti-inflammatory[5] activities. Renewed interest in this natural compound started with the discovery of pimaranes belonging to a class of potent potassium-channel (BK channel) openers.[6] Openers of these channels have emerged as potentially useful agents in the therapy of various diseases associated with both the central nervous system and smooth muscle system, such as acute stroke, epilepsy, psychoses, erectile dysfunction, arterial hypertension, asthma, and bladder hyperactivity. As primary regulators of neuronal excitability, potassium (K^+) channels have been a major research focus in drug discovery and development.[7] Thus, there is now significant interest in the preparation of isopimaric acid derivatives to possibly enhance or alter its biological activity. Oxidative[8,9] and isomeric[10] transformations of **1** in addition to several modifications of the carboxyl group[11,12] have already been described. Accordingly, in light of new isopimaranes containing a nitrogen substituent in the diterpenoid core, we became interested in the targeted preparation of isopimaric acid derivatives through allylic amination reaction of its accessible derivatives.

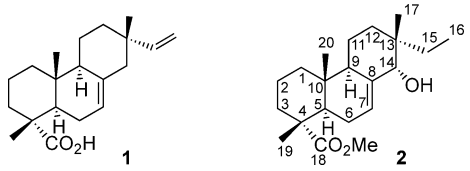

Figure 1. Substrate scope.

The substitution reaction of allylic alcohols with diverse nucleophiles has become an extremely useful tool for the construction of carbon–heteroatom bonds. The direct use of allylic alcohols as substrates, with the hydroxy group as the leaving group and water as the only side product, allows this to be a green reaction with good atom economy.[13] In order to activate the hydroxy functionality as a leaving group, Brønsted acids such as phosphotungstic acid,[14] calix[4]resorcinarene sulfonic acid,[15] or triflic acid[16] and Lewis acids such as transition metal complexes or salts from Fe^{III},[16] Bi^{III},[17] Mo^{VI},[18] Ag^{I},[19] Au^{III},[20] and Au^{I}[19,21] have been used as catalysts. Gold catalysts have recently gained much attention in organic transformations. Reactions catalyzed by gold generally proceed under mild conditions without exclusion of water and oxygen. Both Au^{III} and Au^{I} salts have already been shown to activate allylic alcohols under mild conditions.

In this paper we present a comparative study about the allylic amination reaction of methyl 14α-hydroxy-15,16-dihydroisopimarate (**2**)[9] with different nitrogenated compounds (sub-

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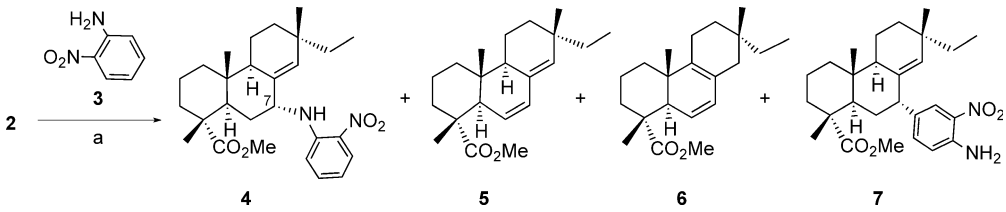
stituted anilines, benzenesulfonamide, *tert*-butyl carbamate) using gold catalysts.

Results and Discussion

The reaction between methyl 14α-hydroxy-15,16-dihydroisopimarate (**2**) and 2-nitroaniline (**3**) was studied using $AuCl_3$, TsOH, or $BF_3{\cdot}Et_2O$ at room temperature in acetonitrile (Scheme 1, Table 1). The first experiment was carried out with 2 mol% of $AuCl_3$ as catalyst giving the expected product **4** in 90% yield (Table 1, entry 1). When TsOH was used as catalyst, even with 10 mol% loading, only 24% of the compound **4** was obtained. Additionally, diterpenoid dienes **5**, **6**, and methyl 7-(4-amino-3-nitrophenyl)-15,16-dihydrosandaracopimarate (**7**) were isolated. In the case of employing of $BF_3{\cdot}Et_2O$ as catalyst (10 mol%), the amination product formation was not observed; only dienes **5** and **6** and the product of electrophilic substitution reaction, **7**, were obtained.

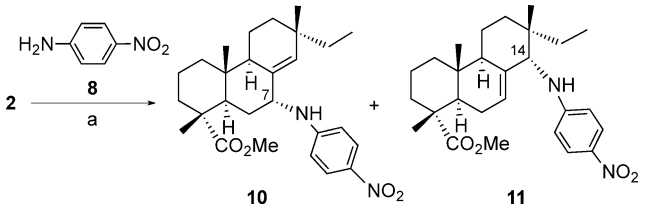


Scheme 1. Amination of methyl 14α-hydroxy-15,16-dihydroisopimarate (**2**) with 2-nitroaniline (**3**). *Reagents and conditions*: a) catalyst, CH_3CN, rt, 24 h. Catalysts and yields are given in Table 1

Table 1. Direct amination of dihydroisopimarate **2** with 2-nitroaniline (**3**).

		Yield [%]			
Entry	Catalyst	Compound **4**	Compound **5**	Compound **6**	Compound **7**
1	$AuCl_3$	90	2	–	–
2	TsOH	24	24	2	8
3	$BF_3{\cdot}OEt_2$	–	28	6	23

We further explored the reactivity of **2** with 4- and 3-nitro-substituted anilines **8** and **9** under the conditions mentioned above (Table 1, Entry 1). We found that the interaction of allylic alcohol **2** with anilines **8** and **9** under the $AuCl_3$ catalyst was not so effective compared with **3**. In the reaction of **2** with 4-nitroaniline (**8**), amination products at the C(7) (compound **10**, 74% yield) and C(14) position (compound **11**, 19% yield) were isolated (Scheme 2).



Scheme 2. $AuCl_3$-catalyzed amination of compound **2** with 4-nitroaniline (**8**). *Reagents and conditions*: a) $AuCl_3$ (2 mol%), CH3CN, rt, 24 h, **10**: 74%, **11**: 19%.

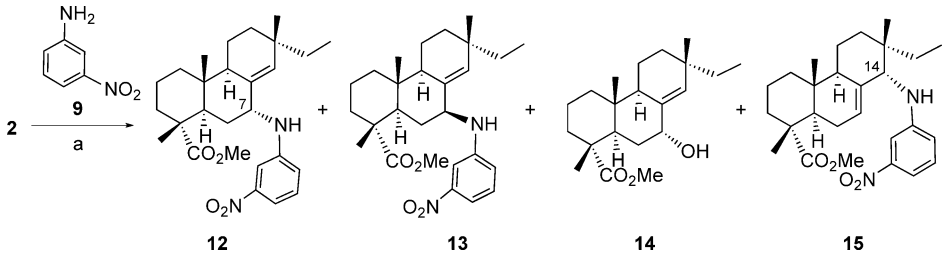
Amination of alcohol **2** with 3-nitroaniline (**9**) in the presence of 2 mol% of catalyst proceeds smoothly to give the desired product **12** only in 24% yield. The 7β-(3-nitroanilino)-15,16-dihydrosandaracopimarate (**13**), the allylic alcohol **14**, and 14α-(3-nitroanilino)-15,16-dihydroisopimarate (**15**) were also isolated. The over-all conversion of this reaction was only at 76% (Scheme 3, Table 2, Entry 1). A further search for more effective catalysts of this reaction was conducted, and some results are summarized in Table 2. The completion of the reaction was increased to 92%, and the amination products **12**, **13**, and **15** compose an over yield of 85% with 6 mol% catalyst loading (Table 2, Entries 1 and 2). The yield of compound **15**—the product of allylic amination of allylic alcohol **14**—was also increased. Exactly the same % conversion was obtained when the reaction was conducted with the catalytic system composed of 2% $AuCl_3$–6% AgOTf (Table 2, Entry 3). However, the reaction was more selective for the formation of 7α-(3-nitroanilino)-substituted diterpenoid (the ratio of **12**:**13** was changed from 4.7:1 to 6.4:1). In the case of employing the mentioned catalyst in nitromethane, a better % conversion and higher isolated yield of the amination product (overall yield of 91%) than in acetonitrile was obtained (Table 2, Entry 4). We were pleased to find that the 7-hydroxydihydrosandaracopimaric acid derivative **14** in this case was not formed.

AgOTf-catalyzed direct amination of primary alcohols was previously described by Shreedar et al.[22] In the presence of this active catalyst, compound **2** reacted with aniline **9** with the formation of the amination products with an overall yield of 68%. The amination reaction of alcohol **2** was considerably promoted also by the addition of $AgBF_4$ (Table 2, Entry 6), while using $AgBF_4$ only resulted in lower reactivity; moreover, a different selectivity of the formation of 7α- and 7β-compounds **12** and **13** (ratio 6.4:1 and 8.5:1) was observed as a function of the used Ag-salt catalyst (Table 2, Entries 5 and 6). Several examples of stereoselective direct amination reaction of alcohols were described by using Au^I-salt catalysts.[19] We found that in the considered reaction with PPh_3AuCl, the catalyst was inactive, but by employing $PPh_3AuCl/AgBF_4$ or PPh_3AuCl/AgOTf catalysts, the amination reaction proceeded with moderate yield and conversion of allylic alcohol **2** (Table 2, Entry 7,8). Increasing of the AgOTf content in the catalytic system provided

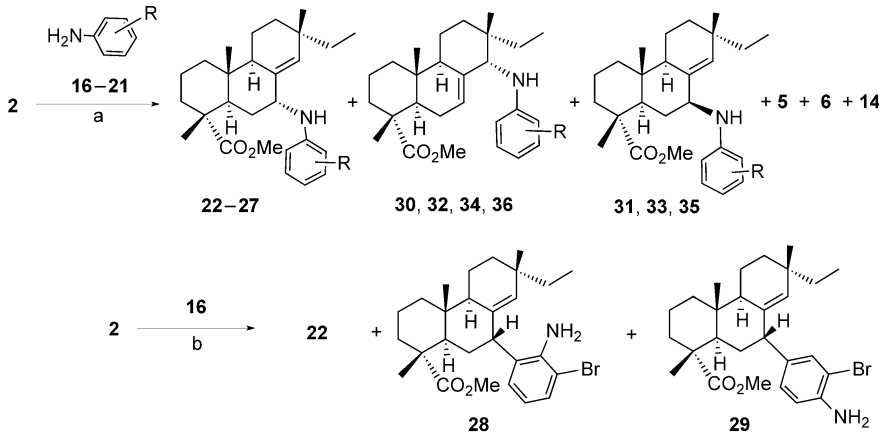
Table 2. Catalyzed amination of isopimarate **2** with 3-nitroaniline (**9**).

Entry	Catalyst (concentration) [mol%]	Yield [%][a] 12	13	14	15	Conversion [%]
1	$AuCl_3$ (2)	24	6	14	13	76
2	$AuCl_3$ (6)	52	11	5	22	92
3	$AuCl_3$ (2)–AgOTf (6)	51	8	9	18	92
4[b]	$AuCl_3$ (2)–AgOTf (6)	63	9	0	19	100
5	AgOTf (6)	45	7	13	16	87
6	$AgBF_4$ (4)	34	4	8	12	62
7	$[PPh_3AuCl]$ (2)–$AgBF_4$(4)	38	8	14	15	77
8	$[PPh_3AuCl]$ (2)–AgOTf(2)	32	5	15	12	80
9	$[PPh_3AuCl]$ (2)–AgOTf(6)	41	9	6	16	96

[a] Isolated yields. [b] Reaction was performed in CH_3NO_2.



Scheme 3. Optimization of reaction conditions. *Reagents and conditions*: a) catalyst, CH_3CN, rt, 24 h. Catalysts, solvents, and yields are given in Table 2



R = 2-Br (**16**, **22**, **30**, **31**); 2-Cl-4-NO_2 (**17**, **23**); 2-NO_2-4-OMe (**18**, **24**); 3-CF_3 (**19**, **25**, **32**, **33**), 4-CF_3 (**20**, **26**, **34**, **35**); 4-C(O)CH_3 (**21**, **27**, **36**)

Scheme 4. Reaction of alcohol **2** with anilines catalyzed by $AuCl_3$–AgOTf. *Reagents and conditions*: a) $AuCl_3$–AgOTf, solvent, rt, 24 h; b) $AuCl_3$–AgOTf, CH_3NO_2, rt, 24 h. Solvents and yields are given in Table 3

Table 3. Direct allylic amination of alcohol **2** with anilines catalyzed by $AuCl_3$–AgOTf.

Entry	Aniline	Solvent	Isolated compounds (yield) [%]
1	**16**	CH_3NO_2	**22** (53); **28** (10); **29** (6)
2	**16**	CH_3CN	**22** (39); **30** (19); **31** (16); **14** (13); **5** (2); **6** (1)
3	**17**	CH_3CN	**23** (52); **6** (14)
4	**18**	CH_3CN	**24** (81); **5** (5); **6** (3)
5	**19**	CH_3NO_2	**25** (48); **32** (20); **33** (13); **5** (2); **6** (2)
6	**20**	CH_3CN	**26** (70); **34** (14); **35** (7); **14** (6)
7	**21**	CH_3NO_2	**27** (67); **36** (11)

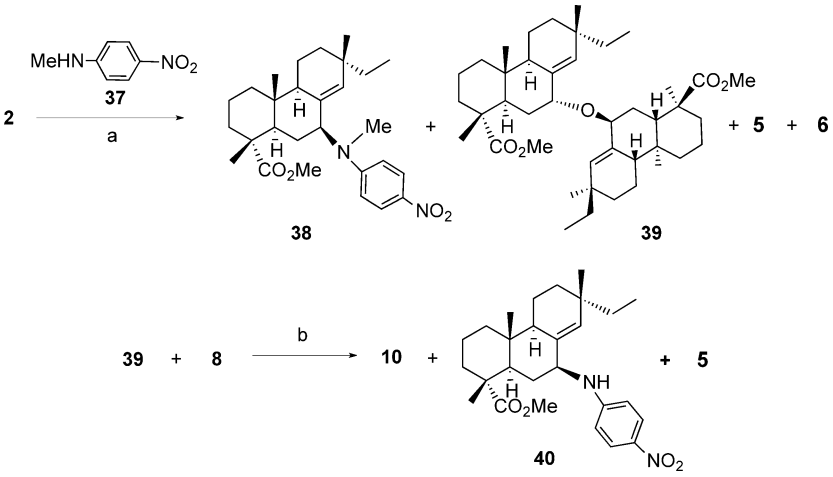
the conversion of compound **2**. $Ph_3PAuOTf$, generated in situ from Ph_3PAuCl and AgOTf, was found to be the best catalyst for the direct amination reaction of methyl 14-hydroxy-15,16-dihydroisopimarate (**2**). The best condition involved the use of a 1:3 mixture of Au^I complex and AgOTf (Table 2, Entry 9), but the stereoselectivity of formation of 7α-(3-nitroanilino)-substituted derivative **12** (ratio **12**/**13** of 4.5:1) was lower than with the use of the $AuCl_3$–AgOTf catalyst (Entries 3,4).

With the optimized conditions in hand (2 mol% $AuCl_3$–6 mol% AgOTf in either nitromethane or acetonitrile), we then extended the scope to various amines by amination of compound **2** with anilines **16**–**21** in this catalytic system (Scheme 4, Table 3). The results revealed that all the desired 7α-anilino-15,16-dihydrosandaracopimaric acid derivatives **22**–**27** could be obtained in high yields (48–81%). We found that the reaction of **2** with 2-bromoaniline **16** in CH_3NO_2 proceeds with the formation of a mixture of amination reaction product **22** and electrophilic substitution reaction products **28** and **29** (Table 3, entry 1). Using acetonitrile as a solution gave the possibility to exclude the reaction of electrophilic substitution. Allylic amination in this case proceeds with lower selectivity; amination products **22**, **30**, and **31**, were isolated with yields of 39, 19, and 16% accordingly. Additionally, compound **14** and dienes **5** and **6** were also isolated. The allylic amination reaction of **2** with anilines **17**, **18**, and **20** with a strong electron-withdrawing group in *o*- or *p*-position to the amino group was performed in acetonitrile; by using nitromethane as a solution, dienes **5** and (or) **6** were obtained as the main products. Reactions of **2** with *o*-,*p*-disubsti-

tuted nitroanilines **17** or **18** in acetonitrile proceed selectively with the formation of 7α-anilinosubstituted derivatives **23** and **24**, respectively (Table 3, Entries 3 and 4); compound **17** displayed lower reactivity in the amination reaction.

By the reaction of compound **2** with 3-substituted aniline **19** in nitromethane, amination products **25**, **32**, and **33** were obtained with the overall yield of 81%; however, the reaction proceeded with lower selectivity (Table 3, Entry 5). The *p*-substituted anilines **20** and **21** afforded the desired amination products **26**, **34**, and **35**, or **27** and **36**, respectively, in good overall yields (Entries 6 and 7).

In light of the results obtained from the optimization of reaction parameters, we decided to further explore the reaction of allylic alcohol **2** using different nitrogenated nucleophiles. Compound **2** was submitted to the direct amination with the more basic *N*-methyl-4-nitroaniline (**37**) (Scheme 5). On the contrary, this reaction in acetonitrile gave rise to the corresponding 7β-amination product **38** (18% yield). Besides dienes **5** (31% yield) and **6** (3% yield), a biditerpenoid derivative **39**

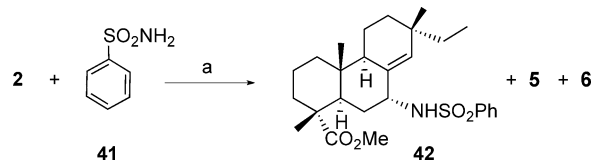


Scheme 5. Amination of alcohol **2** with N-methyl-4-nitroaniline (**37**). *Reagents and conditions*: a) 2% $AuCl_3$–6% AgOTf, CH_3CN, rt, 24 h, **38**: 18%, **39**: 15%, **5**: 31%, **6**: 3% ; b) 2% $AuCl_3$–6% AgOTf, CH_3NO_2, rt, 24 h, **10**/**40** (1:1 ratio): 46%, **5**: 38%.

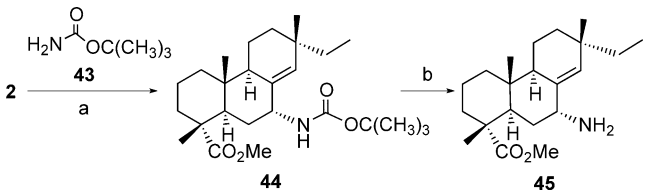
(15% yield) was isolated. Quite interestingly, the reaction of compound **39** with 4-nitroaniline (**8**) in nitrometane proceeds with the formation of two amination products at the C(7) position—compounds **10** and **40** (ratio, 1:1; 46% yield), apart from the diene **5** (38% yield) (Scheme 5).

The reaction of allylic alcohol **2** with benzenesulfonamide (**41**) was also taken into account (Scheme 6). Firstly, the diterpenoid allylic benzenesulfonamide **42** was obtained in 41% yield when acetonitrile was used as the solvent. In addition, dienes **5** and **6** were isolated in 18% yield in approximately a 2:1 ratio. When the reaction was performed in nitromethane, diene **5** was obtained as the main product.

Reaction of alcohol **2** with *tert*-butyl carbamate **43** in nitromethane proceeded with the formation of compound **44** as the only isolable product (65% yield) (Scheme 7). Acidic hydrolysis of **44** smoothly led to the methyl 7α-amino-15,16-dihydrosandaracopimarate (**45**).

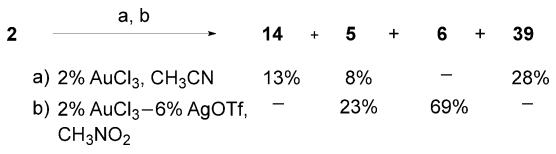


Scheme 6. Reaction of alcohol **2** with benzenesulfonamide (**41**). *Reagents and conditions*: a) 2% $AuCl_3$–6% AgOTf, CH_3CN, rt, 24 h, **42**: 41%, **5**/**6**: 18% (2:1 ratio).



Scheme 7. Reaction of alcohol **2** with *tert*-butyl carbamate (**43**). *Reagents and conditions*: a) 2% $AuCl_3$–6% AgOTf, CH_3NO_2, rt, 24 h, 65%; b) HCl, MeOH, 90%.

Above mentioned experiments of the reaction of 14α-hydroxydihydroisopimarate **2** with anilines **3**, **8**, **9**, **16**–**21**, **37**, benzenesulfonamide (**41**), and *tert*-butyl carbamate (**43**) under the gold catalysts proceeded due to a carbocation intermediate involved in the process. In addition to direct allylic amination reaction, the skeletal transformation of the diterpenoid **2**, as well as reactions with C–H and O–H nucleophiles, were performed. Furthermore, the key tricyclic carbocation might be generated in several isomeric forms (by thermodynamic and sterical access) prior to the amination reaction, because the α- and β-amination products could be formed. Moreover, a rearrangement of the allylic alcohol catalyzed by a Lewis acid could also have an obvious impact on this reaction. In order to confirm this, allylic alcohol **2** was allowed to react under reaction conditions identical to those described above (Table 2, Entries 1 and 4) in the presence of $AuCl_3$ in acetonitrile or $AuCl_3$–AgOTf in nitromethane, and without any nucleophile (Scheme 8). Under $AuCl_3$ action in acetonitrile, the main transformations of **2** included the rearrangement into **14** and the formation of the diterpenoid ether **39** (64% conversion). By



Scheme 8. Transformations of alcohol **2** in the reaction conditions.

the action of $AuCl_3$–AgOTf in CH_3NO_2, compound **2** was transformed into isopimara-6(7),8(14)-diene **5** and isopimara-6(7),8(9)-diene **6**. Interestingly, in these conditions, compound **6** was stable and was not isomerized.

Finally, and with the aim of gaining more knowledge about the amination reaction of the diterpenoid **2**, the allylic alcohol **14** was also made to undergo a direct allylic amination reaction using 3-nitroaniline (**9**) as a nucleophile under the optimized reaction conditions (Table 2, Entry 3). After the reaction time, compounds **12**, **13**, and **15** were obtained in the 51, 15, and 7% yields, respectively (Scheme 9). The same trend in product formation was observed in the amination of allylic alcohol **2** (Table 2, Entry 3). These results point out that the mechanism for this reaction is probably through a nucleophilic S_N1-type process.

The composition and structure of the synthesized compounds were confirmed by infrared (IR) and UV/Vis spectroscopy, ^1H and ^{13}C NMR, mass spectrometry (MS), and X-ray data for compounds **5**, **24**, **27**, and **36**. The ^1H and ^{13}C NMR spectra of all synthesized compounds agreed with their structures and contained one set of characteristic signals for the tricyclic diterpenoid core and the corresponding substituents. The ^{13}C NMR spectra are given in Tables S1–S4 in the Supporting Information. The configuration of the substituent at C7 of the synthesized dihydrosandaracopimaric acid derivatives was unequivocally established from ^1H NMR data. The H7 proton in the ^1H NMR spectra of the 7α-substituted derivatives **4**, **7**, **10**, **12**, **22**–**27**, **28**, **29**, **42**, **44**, and **45** appeared as a doublet of doublets (dd), broad doublet, or broad singlet at 3.39–4.16 ppm, indicating the axial disposition of the substituent. The H7 proton in the spectra of compounds **13**, **31**, **33**, **35**, **38**, and **40** appeared as a dd with *J*ax-ax of 12.2–11.9 Hz and *J*ax-eq of 2.3–3.0 Hz, indicating the equatorial disposition of the aniline substituent. The signals for atom H14 in dihydroisopimaric acid derivatives **11**, **15**, **30**, **32**, **34**, and **36** are found in the range of 3.43–3.57 ppm. The relative configuration of the substituent at the C14 position was confirmed by Nuclear Overhauser Effect spectroscopy (NOESY) spectral data (NOE appeared for H14 and C17-methyl signals; no NOE-effect was observed between H14 and H9 protons). The structures of compounds **5**, **24**, **27**, and **36** were established by X-ray structure analysis. The refined molecules are shown in Figure 2. The X-ray data of compounds and selected hydrogen bond parameters for compounds **24** and **27** are presented in Tables S5 and S6, respectively, in the Supporting Information.

14 + **9** —a→ **12** + **13** + **15**

Scheme 9. Reaction of alcohol **14** with with 3-nitroaniline (**9**). *Reagents and conditions*: a) 2% $AuCl_3$–6% AgOTf, CH_3CN, rt, 24 h, **12**: 51%, **13**: 15%, **15**: 7%.

The bond lengths and bond angles are the same as the statistical values.[23] An envelope-like conformation of the cyclohexene ring C5–C10 of **5** could be characterized by the C10 atom deviation from the plane of the rest of the atoms, which was equal to 0.762(2) (the standard deviation from the mean plane was 0.018 Å). The other cyclohexene ring of **5** had a half-chair conformation: C11 and C12 atoms deviated from C9–C8═C14–C13 fragment plane by −0.441(4) and 0.290(4) Å, respectively (with standard deviations of 0.002 Å). An envelope-like conformation of the cyclohexene rings of **24** and **27** could be characterized by C12-atom deviation from the rest of the atomic plane, equal to 0.649(3) Å for **24** and 0.646(5) Å for **27** (standard deviations of 0.015 Å for **24** and 0.030 Å for **27**). The cy-

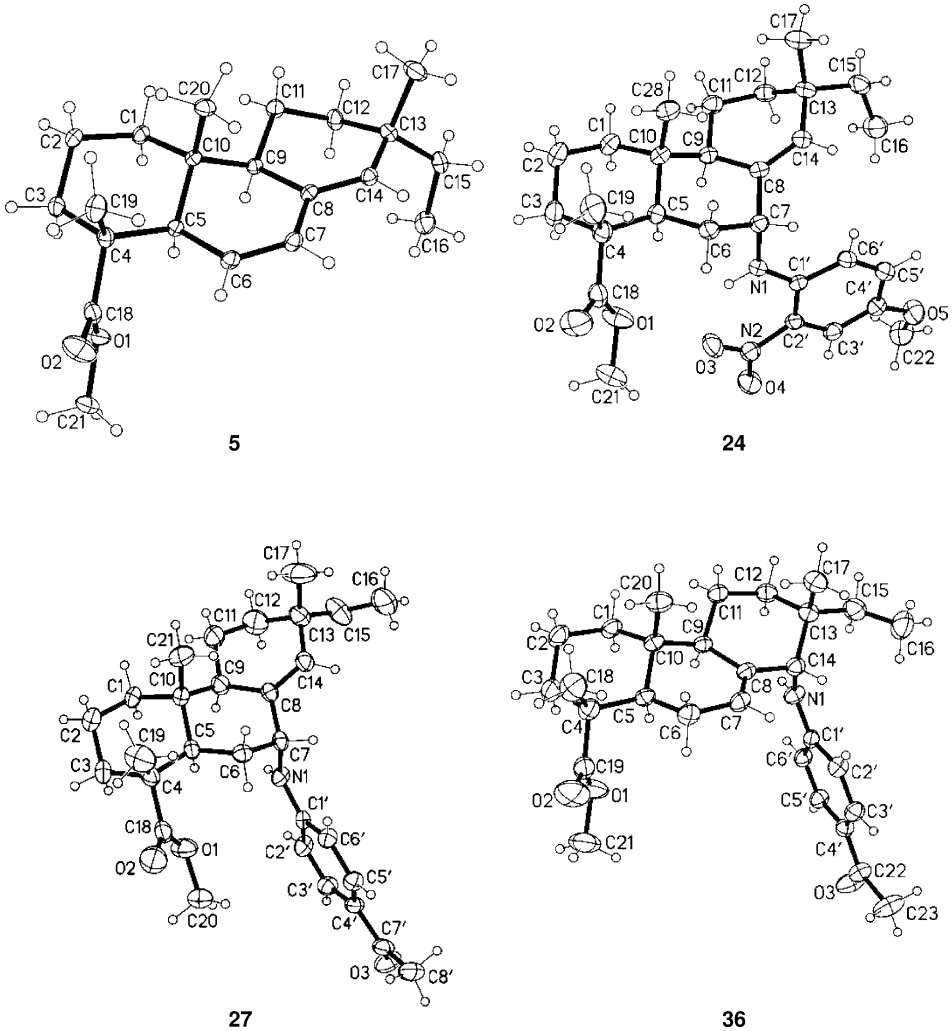


Figure 2. Structures of molecules **5**, **24**, **27**, and **36** in the crystals.

clohexene rings of two crystalographically independent molecules of **36** had a half-chair conformation: for one molecule, C5 and C10 atoms deviated from the C9–C8=C14–C13 fragment plane by −0.520(5) and 0.329(5) Å, respectively (with standard deviations of 0.015 Å). For the other molecule, the C5 and C10 atoms deviated from the C9–C8=C14–C13 fragment plane by −0.394(4) and 0.420(4) Å, respectively (with standard deviations of 0.009 Å).

The crystal structure of **24** was stabilised by a large number of C–H···O1 and C–H···O2 short intermolecular contacts and the N1–H···O3 hydrogen bond. In addition to the H-bond, the C3–H···π interaction with the phenyl ring were observed, showing an atom-to-centroid distance of 2.65 Å. The crystal structure of **27** was stabilised by the many C–H···O2, C–H···O3, and C–H···O5 short intermolecular contacts. Atoms N1 and N2 were are not involved in the intermolecular interactions because of the very short intramolecular N1···N2 and N1···O3 contacts. The two crystalographically independent molecules of **36** formed dimers by N1–H···O2 and N1–H···O3 hydrogen bonds. In addition to the H-bond, the crystal structure of **36** was stabilized by C–H···O1 short intermolecular contact. Interestingly, there weren't any short intermolecular contacts in the crystal structure of **5**, but, in turn, the O1 and O2 atoms were engaged in the C–H···O intramolecular interactions (Table S6 in the Supporting Information).

Conclusion

We have demonstrated that the gold-catalyzed amination of methyl 14α-hydroxy-15,16-dihydroisopimarate with substituted anilines, benzenesulfonamide, or *tert*-butyl carbamate produces good to excellent yields of nitrogen-containing tricyclic diterpenoids, which are extremely useful synthetic intermediates in the construction of biologically important compounds. The stereochemical result of the reaction is dependent on the nature of the nucleophile.

Experimental Section

The experimental details for each compound, including the full chemical names, physical characteristics, and ^{13}C NMR, ^{1}H NMR, IR, UV/Vis, and MS data are available in the Supporting Information.

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