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Gold-Catalyzed Formal (3+2) Cycloaddition in an Ionic Liquid: Environmentally Friendly and Stereoselective Synthesis of Polysubstituted Indanes from Benzylic Alcohols and 1-Phenylpropenes

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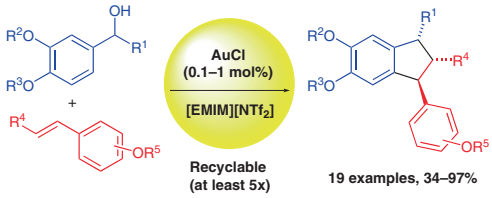

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Abstract A gold-catalyzed formal (3+2) cycloaddition of benzylic alcohols with 1-phenylpropenes in an ionic liquid permits the environmentally friendly stereoselective synthesis of polysubstituted indanes in good yields and with high selectivity. The gold catalyst can be recycled at least five times.

Key words gold catalysis, ionic liquids, (3+2) cycloaddition, indanes, benzylic alcohols, propenylbenzenes

The efficient synthesis of polysubstituted indanes is of great importance because of their potent and diverse biological activities.[1] Examples include diaporindene A[2] (anti-inflammatory activity), asarone dimer[3] (insect-growth regulator, fungicide, insecticide, sedative, and hyperthermic agent), and enrasentan[4,5] (antagonist of nonpeptide endothelin receptors) (Figure 1).

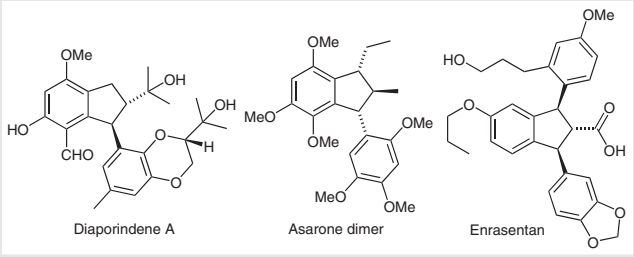
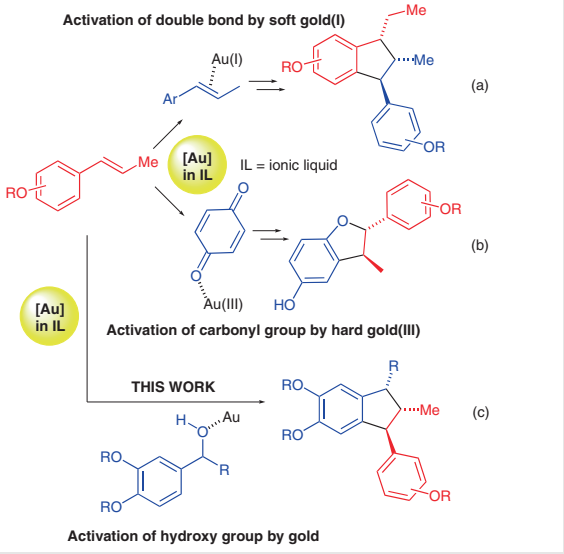


Figure 1 Natural and synthetic polysubstituted indanes

Therefore, much effort has been directed at the development of efficient synthetic pathways to polysubstituted indanes.[6,7] Reported methods include dimerization[8] of 1-phenylpropenes and the formal (3+2) cycloaddition[9,10] of benzylic alcohols with 1-phenylpropenes. However, these methods often require the use of a stoichiometric amount of a reagent ($BF_3{\cdot}OEt_2$ or $SnCl_4$), and a toxic volatile halogenated solvent (CH_2Cl_2 or $CHCl_3$) is employed in many cases. Consequently, there is a need to develop methods that use environmentally benign solvents and sustainable (recyclable) reagents to advance green chemistry.

We recently reported an environmentally friendly and stereoselective synthesis of cyclic compounds (1,2,3-trisubstituted indanes[11] and 2-aryl-3-methyl-dihydrobenzofurans[12]) by the strategic use of a π-philic (soft) gold(I) catalyst and an oxophilic (hard) gold(III) catalyst[13] in an ionic liquid[14] (Scheme 1). Thus, treatment of 1-phenylpropenes



Scheme 1 (a) Gold-catalyzed dimerization of 1-phenylpropenes (previous work). (b) Formal (3+2) cycloaddition of *p*-quinones with 1-phenylpropenes (previous work). (c) Formal (3+2) cycloaddition of benzylic alcohols with 1-phenylpropenes (this work).

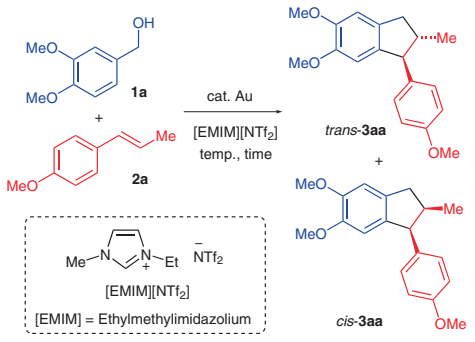
with a soft gold(I) catalyst (AuCl) resulted in dimerization to furnish 1,2,3-trisubstituted indanes with good stereoselectivity, due to activation of the double bond of 1-phenylpropenes by coordination of gold(I) (Scheme 1a). In contrast, similar treatment of 1-phenylpropenes and *p*-quinones with a hard gold(III) catalyst induced formal (3+2) cycloaddition to afford 2-aryl-3-methyldihydrobenzofurans with high stereoselectivity, due to activation of the carbonyl oxygen of the *p*-quinone by coordination to gold(III), even in the presence of 1-phenylpropenes (Scheme 1b). Moreover, recycling of the gold catalyst/ionic liquid was achieved in both reactions (Schemes 1a and 1b).

As a part of our continuing research on environmentally friendly gold-catalyzed reactions, we next focused on the formal (3+2) cycloaddition of benzylic alcohols with 1-phenylpropenes in an ionic liquid to prepare polysubstituted indanes (Scheme 1c). Here, we report a gold-catalyzed, environmentally friendly, stereoselective synthesis of polysubstituted indanes in an ionic liquid through a formal (3+2) cycloaddition of benzylic alcohols with 1-phenylpropenes. This reaction is advantageous from both environmental and economic points of view, as it does not require the use of a toxic volatile halogenated solvent or a stoichiometric amount of reagent, and the gold catalyst/ionic liquid can be recycled several times.

Initially, we investigated the formal (3+2) cycloaddition of 3,4-dimethoxybenzyl alcohol (**1a**) with *trans*-anethole (**2a**) in 3-ethyl-1-methyl-1*H*-imidazol-3-ium bis(trifluoromethylsulfonyl)imide ([EMIM][NTf_2]) in the presence of a gold catalyst that can activate the hydroxy group of **1a** (Table 1). The gold(III) catalyst $AuBr_3$ afforded the desired indane **3aa** in a moderate yield with great selectivity (Table 1, entries 1–3), whereas the gold(I) catalyst AuCl (1 mol%) furnished **3aa** in a good yield with high selectivity (entry 4). In terms of both yield and stereoselectivity, AuCl (1 mol%) in the ionic liquid appeared to be the best catalyst for this reaction.

NMR spectroscopic data supported the formation of a 1,2-disubstituted indane *trans*-**3aa**, and the expected structure was confirmed by means of X-ray crystal-structure analysis of **3aa** (Figure 2).[15] Reactions in other solvents ([EMIM][AcO], [EMIM][BF_4], [EMIM][$MeSO_4$], or [EMIM][$(MeO)_2PO_2$]) gave little or no **3aa**. In the case of the reaction with AuCl (1 mol%), the use of an organic solvent (Dichroloethane:DCE) reduced the yield of **3aa** to 35% and increased the reaction time to 77 hours (entry 3 vs entry 5). Lee's group has reported various advantages of ionic liquids for catalytic reactions, including the formation of more-reactive catalysts and the stabilization of reactive intermediates and transition states.[16] Although the precise reason for the high activity of AuCl in [EMIM][NTf_2] (entry 4) remains unclear, two possibilities can be considered. The first is that an active gold species, $AuNTf_2$, might be generated by anion exchange between the chloride ion of the gold catalyst and the NTf_2 ion of the ionic liquid [EMIM][NTf_2]. The second possibility is the formation of a reactive gold species bearing an *N*-heterocyclic carbene ligand,[17] which might be generated from the EMIM cation of [EMIM][NTf_2].

Table 1 Optimization of the Reaction Conditions for the Gold-Catalyzed Formal (3+2) Cycloaddition of Benzylic Alcohol **1a** with *trans*-Anethole (**2a**)



Entry	Catalyst (mol%)	Temp (°C)	Time (h)	Yield (%) of **3aa** (*trans*/*cis*)
1	$AuBr_3$ (5)	rt	0.5	58 (98:2)
2	$AuBr_3$ (2)	rt	1.5	64 (98:2)
3	$AuBr_3$ (1)	60	0.5	64 (98:2)
4	AuCl (1)	60	0.5	75 (96:4)
5[a]	AuCl (1)	60	77	35 (96:4)

[a] The reaction was carried out in DCE.

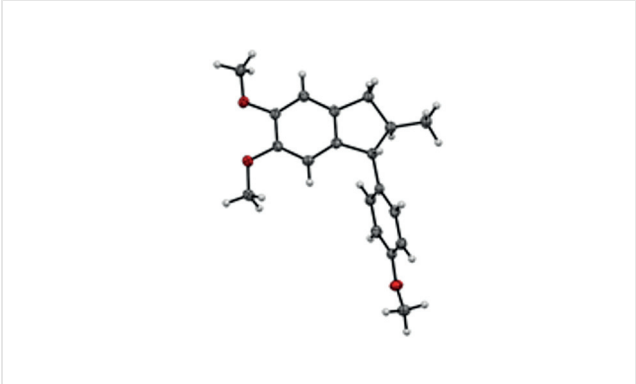
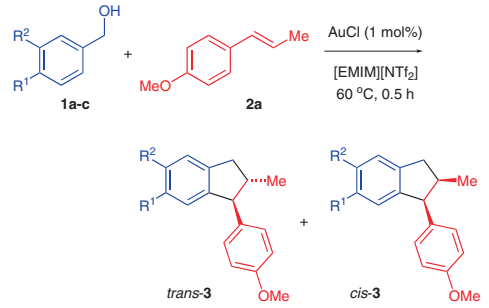


Figure 2 X-ray crystal structure of the 1,2-disubstituted indane *trans*-**3aa**

To examine the effect of ring substituents on the benzylic alcohol **1**, we conducted the gold-catalyzed formal (3+2) cycloaddition of benzylic alcohols **1a–c** with *trans*-anethole (**2a**) (Table 2). Whereas the reaction of benzylic alcohol **1a**, bearing two methoxy groups, afforded a good yield of **3aa** (Table 2, entry 1), the reaction of benzylic alcohol **1b** having one methoxy group afforded only a trace of the corresponding product **3ba** (entry 2). In the case of ben-

Table 2 Effect of Substituents on Benzylic Alcohols **1a–c** on the Gold-Catalyzed Formal (3+2) Cycloaddition

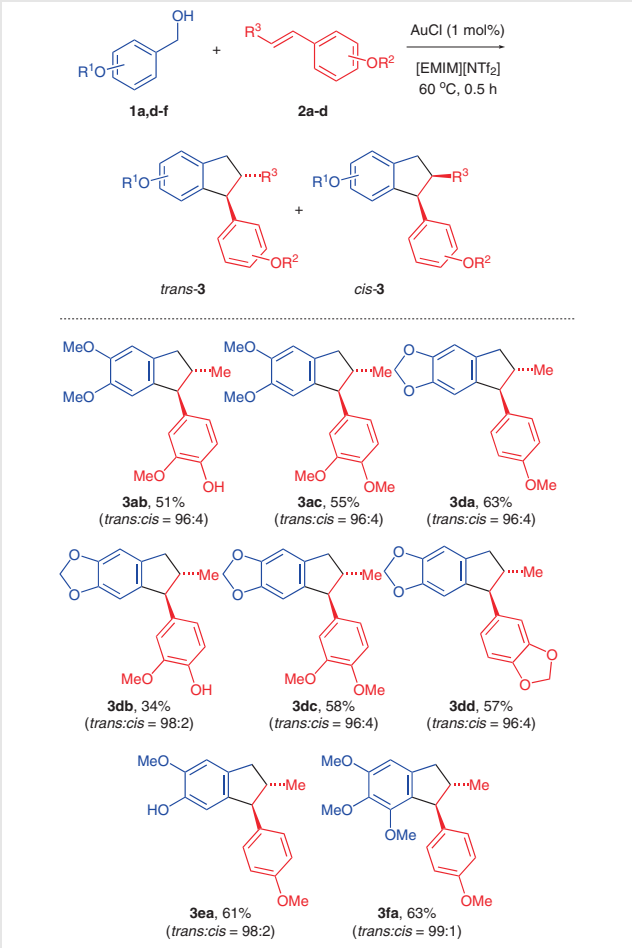


Entry	1	R^1	R^2	Product	Yield (%) (*trans*/*cis*)
1	**1a**	MeO	MeO	**3aa**	75 (96:4)
2	**1b**	MeO	H	**3ba**	trace
3	**1c**	H	H	–	–

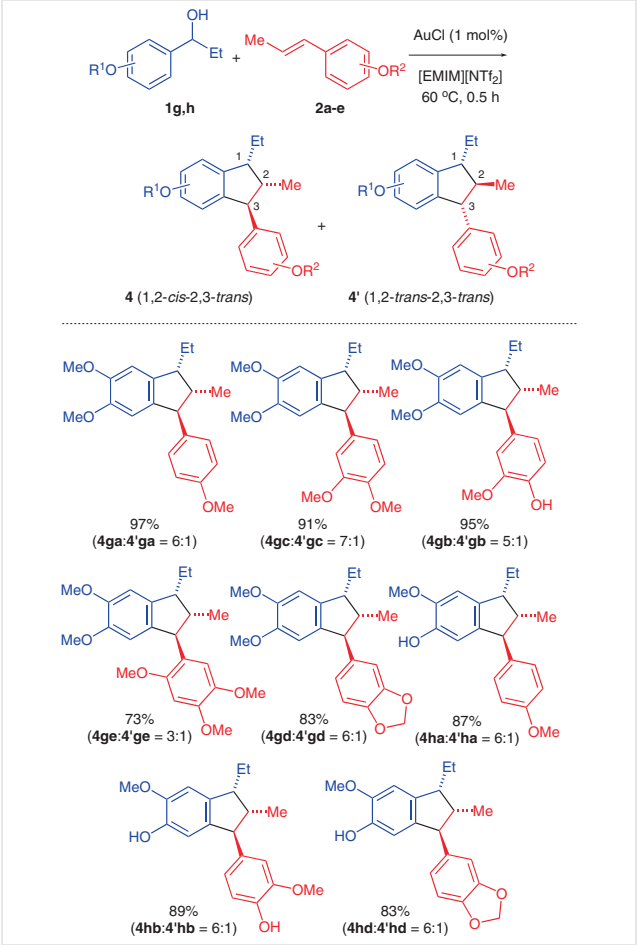
zyl alcohol (**1c**), bearing no methoxy group on the ring, no product was obtained (entry 3). Thus, the presence of two methoxy groups on the aromatic ring of the benzylic alcohol **1a** appears to be required to obtain indane **3aa**.

Next, we investigated the scope of the gold-catalyzed formal (3+2) cycloaddition for the synthesis of disubstituted indanes **3** by using various benzylic alcohols **1a** and **1d–f** and 1-phenylpropenes **2a–d** in the presence of 1 mol% AuCl in the ionic liquid [EMIM][NTf_2] (Scheme 2). Various combinations of **1a** or **1d–f** with **2a–d** afforded the corresponding products **3** in moderate to good yields with high selectivity, even in the presence of various oxygen-containing functional groups on the substrates.

In addition, we extended the procedure to prepare 1,2,3-trisubstituted indanes **4** (Scheme 3). Treatment of benzylic alcohols **1g** and **1h** bearing an ethyl group at the benzylic position with 1-phenylpropenes **2a–e** in the presence of 1 mol% AuCl in the ionic liquid [EMIM][NTf_2] afforded the corresponding 1,2,3-trisubstituted indanes **4** in high



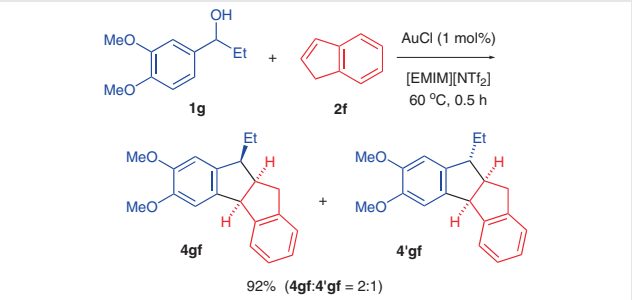
Scheme 2 Scope of the gold-catalyzed formal (3+2) cycloaddition of benzylic alcohols **1a** and **1d–f** with 1-phenylpropenes **2a–d**



Scheme 3 Gold-catalyzed formal (3+2) cycloaddition of benzylic alcohols **1g** and **1h** with 1-phenylpropenes **2a–e** in an ionic liquid to give 1,2,3-trisubstituted indanes **4**

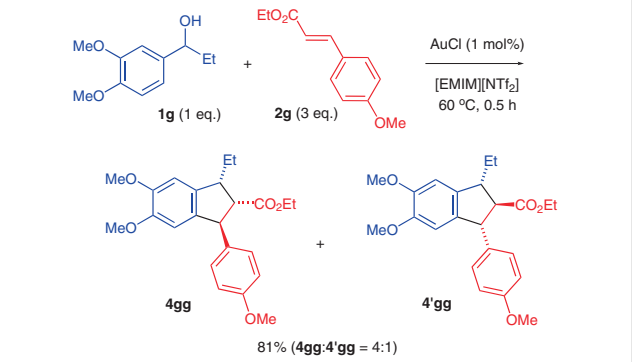
yields with good selectivity.[18] Interestingly, the yields of the 1,2,3-trisubstituted indanes **4** in this reaction were generally higher than those of the 1,2-disubstituted indanes **3**.

In the case of indene (**2f**), the gold-catalyzed formal (3+2) cycloaddition with benzylic alcohol **1g** afforded the corresponding indane **4gf** in high yield, albeit with low stereoselectivity (Scheme 4).



Scheme 4 Gold-catalyzed formal (3+2) cycloaddition of benzylic alcohol **1g** with indene (**2f**)

In addition, even when the methyl group at the 2-position of 1-phenylpropene **2** was replaced with an ester group (**2g**), the reaction proceeded to give the corresponding indane **4gg** (Scheme 5). Although the use of one equivalent of ethyl *trans*-*p*-methoxycinnamate (**2g**) in the reaction resulted in a moderate yield, the use of three equivalents of **2g** furnished the desired product **4gg** in a good yield.[19] The ester group in indane **4gg** could be a useful functionality for further elaboration.



Scheme 5 Gold-catalyzed formal (3+2) cycloaddition of benzylic alcohol **1g** with ethyl *trans*-*p*-methoxycinnamate (**2g**)

The structure of **4gg** was definitively established by means of X-ray crystal structure analysis (Figure 3).[20]

We next conducted a large-scale preparation of indane **3aa** and we examined the effect of a reduced amount of the gold catalyst (Scheme 6). The large-scale preparation of 1,2-disubstituted indane **3aa** was achieved from 1.0 g (6.0 mmol) of benzylic alcohol **1a** and *trans*-anethole (**2a**), affording the product **3aa** in 73% yield.[21] Moreover, even when the amount of AuCl was reduced to 0.1 mol%, the reaction proceeded smoothly over a slightly longer reaction time (5 h) to give the desired product **3aa** in good yield with high selectivity.

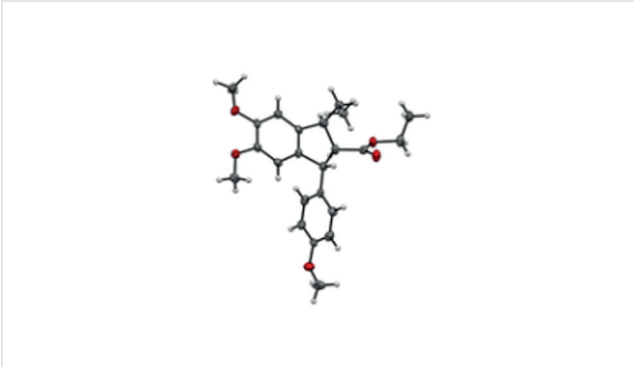
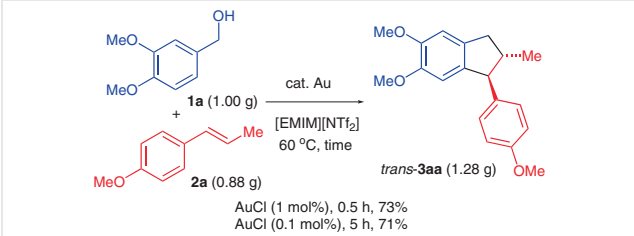


Figure 3 X-ray crystal structure of 1,2,3-trisubstituted indane **4gg**

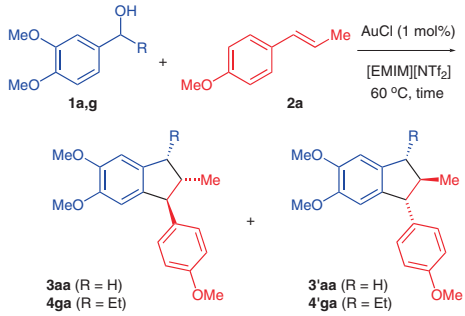


Scheme 6 Large-scale preparation of indane **3aa** and the effect of a reduced amount of the gold catalyst (0.1 mol%)

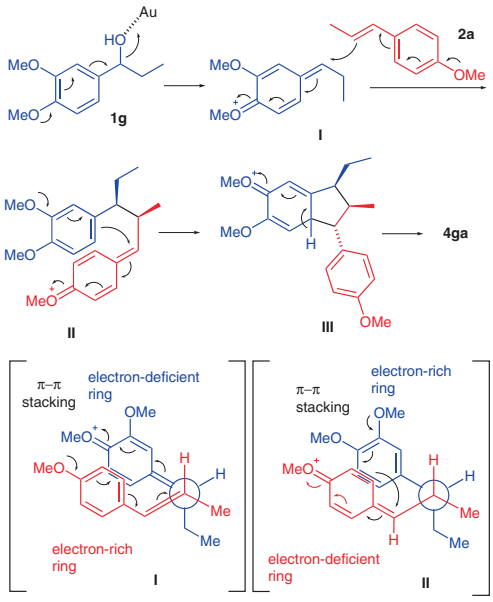
Finally, recycling of the gold catalyst in ionic liquid [EMIM][NTf_2] was investigated. In the reactions of benzylic alcohols **1a** and **1g** with *trans*-anethole (**2a**), the AuCl (1 mol%) and ionic liquid [EMIM][NTf_2] could be recycled at least five times with only slight loss of activity (Table 3).[22]

A plausible mechanistic model for the reaction of benzylic alcohol **1g** with *trans*-anethole (**2a**) in [EMIM][NTf_2] is shown in Scheme 7. The gold species coordinates to the oxygen atom of the benzylic alcohol **1g**, forming active intermediate **I**. Addition of *trans*-anethole (**2a**) to the active intermediate **I** affords intermediate **II** bearing an electron-rich aromatic ring and an electron-deficient ring. Cyclization takes place between the aromatic ring and the benzylic position in intermediate **II** to furnish intermediate **III**, which undergoes aromatization to provide indane **4ga** with good selectivity (1,2-*cis*-2,3-*trans*). The first C–C bond formation (addition step, **I** → **II**) would be important in controlling the stereochemistry. In the addition step, π–π stacking between the electron-rich ring and the electron-deficient ring in intermediate **I** would make the orthogonal approach favorable, leading to the formation of a 1,2-*cis* configuration. Cyclization proceeds again under the influence of π–π stacking in intermediate **II** to form a five-membered ring with a 1,2-*cis*-2,3-*trans* stereochemistry.

Table 3 Recycling of the Gold Catalyst and Solvent in the Formal (3+2) Cycloaddition of Benzyl Alcohols **1a** and **1g** with *trans*-anethole (**2a**)



Run	Time (h)	Yield (%) (**3aa**/**3′aa**)	Time (h)	Yield (%) (**4ga**/**4′ga**)
1	0.5	75 (96:4)	0.5	97 (6:1)
2	20	58 (96:4)	22	81 (6:1)
3	20	66 (95:5)	22	79 (6:1)
4	22	57 (96:4)	24	73 (6:1)
5	24	48 (96:4)	24	71 (6:1)



Scheme 7 Plausible reaction mechanism for the gold-catalyzed formal (3+2) cycloaddition of benzylic alcohol **1g** and *trans*-anethole (**2a**)

In summary, we have developed a stereoselective, gold-catalyzed formal (3+2) cyclization of benzylic alcohols **1** with 1-phenylpropenes **2** in the ionic liquid [EMIM][NTf_2]. This reaction provides an environmentally friendly alternative for the synthesis of a variety of polysubstituted indanes. We are currently pursuing further applications of this environmentally benign and sustainable catalyst system.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-2002-4122.

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(18) There are four possible diastereomers for 1,2,3-trisubstituted indanes **4**, namely, α-(1,2-*cis*-2,3-*trans*), β-(1,2-*cis*-2,3-*cis*), γ-(1,2-*trans*-2,3-*trans*), and δ-(1,2-*trans*-2,3-*cis*), as shown below in Figure 4. The stereochemical assignment of the 1,2,3-trisubstituted indanes **4** was based on ^{1}H NMR spectra, chemical shifts (ppm), coupling constants (*J* values), and the application of double-irradiation techniques. MacMillan *et al.* reported *J* values for the α-(1,2-*cis*-2,3-*trans*) and γ-(1,2-*trans*-2,3-*trans*) configurations of 1,2,3-trisubstituted indanes **4** (see ref. 8a). Lantaño *et al.* also reported similar chemical shifts (ppm) and coupling constants (*J* values) for the α-(1,2-*cis*-2,3-*trans*) and γ-(1,2-*trans*-2,3-*trans*) configurations of 1,2,3-trisubstituted indanes **4** (see ref. 9e).

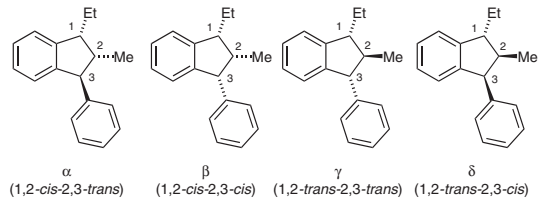

Figure 4

(19) **Ethyl (1*R**,2*S**,3*S**)- and (1*R**,2*R**,3*R**)-1-Ethyl-5,6-dimethoxy-3-(4-methoxyphenyl)indane-2-carboxylate (4gg and 4′gg)**

1 mol% AuCl (1.2 mg, 0.0051 mmol) was added at rt to a solution of benzylic alcohol **1g** (100 mg, 0.51 mmol) and ethyl *trans*-*p*-methoxycinnamate (**2g**) (315 mg, 1.53 mmol) in [EMIM][NTf_2] (1 mL). When benzylic alcohol **1g** was completely consumed (TLC; usually <30 min), the product was extracted with Et_2O and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexane–EtOAc) to give **4gg** and **4′gg** as a colorless oil; yield: 158 mg (81%, 4:1).

IR (KBr): 2958, 2933, 2833, 1728, 1609, 1510, 1500, 1463 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.18 (d, *J* = 8.7 Hz, 2 H × 4/5)*, 7.13 (d, *J* = 8.7 Hz, 2 H × 1/5), 6.88 (d, *J* = 8.7 Hz, 2 H × 1/5), 6.86 (d, *J* = 8.7 Hz, 2 H × 4/5)*, 6.78 (s, 1 H × 4/5)*, 6.75 (s, 1 H × 1/5), 6.41 (s, 1 H × 4/5)*, 6.38 (s, 1 H × 1/5), 4.75 (d, *J* = 9.9 Hz, 1 H × 4/5)*, 4.52 (d, *J* = 9.3 Hz, 1 H × 1/5), 4.16 (q, *J* = 7.2 Hz, 2 H × 4/5)*, 4.14 (q, *J* = 7.2 Hz, 2 H × 1/5), 3.91 (s, 3 H × 4/5)*, 3.91 (s, 3 H × 1/5), 3.83 (s, 3 H × 1/5), 3.81 (s, 3 H × 4/5)*, 3.74 (s, 3 H × 4/5)*, 3.73 (s, 3 H × 1/5), 3.52–3.45 (m, 1 H × 1/5), 3.41 (t, *J* = 8.1 Hz, 1 H × 4/5)*, 3.41–3.34 (m, 1 H × 4/5)*, 2.86 (t, *J* = 9.0 Hz, 1 H × 1/5), 2.09–1.98 (m, 1 H × 1/5), 1.80–1.50 (m, 2 H × 4/5)*, 1.27 (t, *J* = 7.2 Hz, 3 H × 4/5)*, 1.23 (t, *J* = 7.2 Hz, 3 H × 1/5), 0.99 (t, *J* = 7.5 Hz, 3 H × 1/5), 0.96 (t, *J* = 7.5 Hz, 3 H × 4/5)*. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.0, 172.6*, 158.5, 158.4*, 148.8, 148.7*, 148.1*, 136.71*, 136.67*, 136.6, 136.2, 135.8, 135.5*, 129.7*, 129.3, 113.9, 113.8*, 108.1*, 107.8*, 107.7, 106.3, 60.7, 60.5, 60.3*, 60.2*, 56.1*, 56.0*, 55.2*, 53.9, 50.7*, 48.8, 47.7*, 26.5, 24.6*, 14.3*, 11.7*, 10.6. HRMS (EI): *m/z* [M^+] calcd for $C_{23}H_{28}O_5$: 384.1937; found: 384.1935.

(20) CCDC 2223279 contains the supplementary crystallographic data for compound **4gg**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures

(21) **5,6-Dimethoxy-1-(4-methoxyphenyl)-2-methylindane (3aa); Enlarged-Scale Procedure**
1 mol% AuCl (14 mg, 0.060 mmol) was added at rt to a solution of benzylic alcohol **1a** (1.0 g, 6.0 mmol) and ethyl *trans*-anethole (**2a**) (0.88 g, 6.0 mmol) in [EMIM][NTf_2] (5 mL). When benzylic alcohol **1a** was completely consumed (TLC; usually <30 min), the product was extracted with Et_2O and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexane–EtOAc) to give a colorless oil; yield: 1.3 g (73%).
IR (KBr): 3033, 299, 2931, 2837, 1614, 1512, 1472, 1446, 1512, 1471, 1445, 1410, 1313, 1213, 1173, 1088, 1028, 995, 856, 820, 804, 764 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.11 (d, *J* = 8.7 Hz, 2 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 6.79 (s, 1 H), 6.39 (s, 1 H), 3.88 (s, 3 H), 3.81 (s, 3 H), 3.72 (s, 3 H), 3.70 (d, *J* = 9.5 Hz, 1 H), 3.06 (dd, *J* = 14.9, 7.5 Hz, 1 H), 2.55 (dd, *J* = 14.9, 9.5 Hz, 1 H), 2.42–2.30 (m, 1 H), 1.17 (d, *J* = 6.6 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.2, 148.14, 148.07, 138.3, 136.4, 135.2, 129.4, 113.8, 108.1, 107.4, 58.9, 56.1, 56.1, 55.2, 46.9, 40.1, 18.4. HRMS (EI): *m/z* [M^+] calcd for $C_{19}H_{22}O_3$: 298.1569; found: 298.1569.

(22) In the recycling of the gold catalyst in this reaction, the reaction time was prolonged after the first cycle. The cause is assumed to be imidazole, which is a decomposition product generated when water produced during the reaction reacts with the ionic liquid in the presence of the gold catalyst.[23] The generated imidazole might coordinate to the gold catalyst, significantly reducing its activity and prolonging the reaction time; however, this has not been confirmed.

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