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Cocyclotrimerization of 6-Alkynylpurines with α,ω-Diynes as a Novel Approach to Biologically Active 6-Arylpurines

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Transition metal complex catalyzed cocyclotrimerization of 6-alkynylpurines **1** with various diynes enables the preparation of a plethora of substituted 6-arylpurines **3** in good yields. The most general catalyst for the reaction is a user-friendly system based on a nickel−phosphine complex and reductant ($NiBr_2$(dppe)/Zn) in MeCN. The reaction conditions are compatible with various protective groups on the purine moiety (Bn, THP). As far as other potential catalysts were concerned, only $CoBr(PPh_3)_3$ showed reasonable activity in cocyclotrimerization of alkynylpurines with dipropargyl ether. A comparison of catalytic with stoichiometric approaches and the ligand effect in the catalyst is also given. Cytostatic activity screening of title 6-arylpurines was performed and several moderately active compounds were found.

Introduction

6-Arylpurine derivatives display diverse types of biological activity: some substituted 6-arylpurine bases are antagonists of corticotropin-releasing hormone[1] or possess antimycobacterial and antibacterial activity,[2] while 6-arylpurine ribonucleosides are potent cytostatics.[3] Moreover, 6-arylpurines were used as unnatural nucleobases in artificial base-pairs[4] and as covalent base-pair analogues.[5] So far, biological activity screening and other applications (e.g., in chemical biology) were limited to easily available purines bearing simple aryl groups, while those bearing highly substituted and/or functionalized aryl moieties still remain to be explored. Recently, many bulky and hydrophobic aryl C-nucleosides were also used[6] as potential nucleobase surrogates in extension of the genetic alphabet, also 6-arylpurines bearing bulky hydrophobic substituents are of particular interest.

6-Arylpurines have been efficiently prepared by cross-coupling reactions[7] of 6-halopurines with various organometallics.[8] However, these methods are limited by availability, reactivity, and stability of the corresponding aryl-organometallic reagent. Therefore, it is still of general interest to develop alternative methods for the preparation of some (in particular highly substituted) 6-arylpurines. Structural analysis of a 6-arylpurine reveals that its aryl moiety could be conveniently assembled from a 6-alkynylpurine and a diyne (Scheme 1). Over the years, it has been demonstrated that a transition-metal complex-

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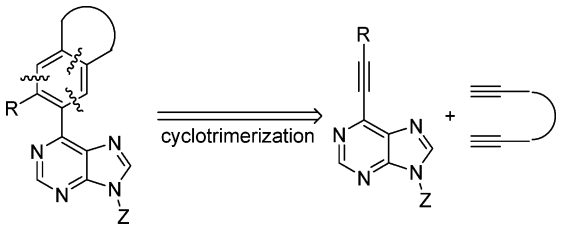
SCHEME 1. Retrosynthetic Analysis of 6-Arylpurines



R = various substituents, Z = a protecting group

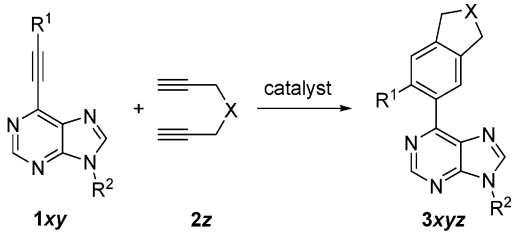
catalyzed cyclotrimerization of alkynes to benzene derivatives is one of the most powerful methods for multiple C−C bond formation that enables variously substituted molecular fragments to be assembled together in a single synthetic operation into a molecule with a high degree of complexity.[9] Therefore, [2 + 2 + 2]-cocyclotrimerization of 6-alkynylpurines with other alkynes or diynes was an alternative hitherto unexplored strategy for the synthesis of 6-arylpurines that could not only be complementary to the cross-coupling procedures but also allow a single-step preparation of products that would be otherwise difficult to synthesize. Such a strategy not only secures rapid and straightforward access to the arylpurines, but the use of simple reactants keeps the overall approach flexible enough to allow also future syntheses of other members of this class of purines or derivatives thereof. In addition, the underlying reactants (diynes and alkynylpurines) themselves can be assembled from readily available building blocks through simple reactions.

Recently, we have communicated early results regarding a novel approach to synthesis of 9-benzyl-6-arylpurines based on transition-metal catalyzed cocyclotrimerizations of 6-alkynylpurines with α,ω-diynes.[10] In this article, we report a full account of the synthesis of 9-benzyl- and 9-THP-6-arylpurines, results of catalysts and the ligand effect on the course of cyclotrimerization, cyclotrimerization in the presence of a stoichimetric amount of Ni complexes, deprotection of 9-THP-6-arylpurines to free purine bases, and the significant cytostatic activity of some highly substituted 6-arylpurines.

Results and Discussion

Cocyclotrimerizations of 9-Bn-6-Alkynylpurines. In our preliminary report,[10] we reported the first example of cocyclotrimerization of 9-benzyl-6-alkynylpurines **1*x*a** with diversely substituted α,ω-diynes **2** (Scheme 2). An

SCHEME 2. Cocyclotrimerization of 6-Alkynylpurines with α,ω-Diynes



1*xy* **2*z*** **3*xyz***

In compounds **1-3**:

x	*y*	*z*
a, R^1 = H	**a**, R^2 = Bn	**a**, X = $C(COOEt)_2$
b, R^1 = Bu	**b**, R^2 = THP	**b**, X = C(COOEt)COMe
c, R^1 = Ph	**c**, R^2 = H	**c**, X = $C(COMe)_2$
		d, X = O
		e, X = CH_2
		f, X = CH_2CH_2
		g, X = C(COOEt)CN

essential part of this project was to study cyclotrimerization activity of various transition metal complexes that have been commonly used for such a process. The obtained results were rather surprising because Wilkinson's catalyst ($RhCl(PPh_3)_3$), which is known to efficiently catalyze cyclotrimerizations,[11−14] failed to catalyze this reaction. Gratifyingly, the rarely used $CoBr(PPh_3)_3$[14−16] proved to be an effective catalyst for cocyclotrimerization of dipropargyl ether with 6-alkynylpurines. The most effective catalysts for cocyclotrimerization proved to be Ni(II) complexes with bidentate or monodentate phosphine ligands [$NiX_2(L)_n$] in combination with Zn powder as a reductant. In this regard, $NiBr_2$(dppe) complex (dppe = bis(diphenylphosphino)ethane) proved to be the catalyst of choice. (Recently, $NiBr_2$(dppe) has been successfully applied as a catalyst in several related cycloaddition reactions.)[17] It is noteworthy that this approach avoids manipulation with highly air- and moisture-sensitive Ni(0) compounds that have been widely used for cyclo-

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trimerizations,[18−20] because the catalytically active Ni(0) species are generated "in situ" from air- and moisture-stable Ni(II) complexes. As far as catalyst loading is concerned, it was found that 20 mol % catalysts is required for the successful completion of the reaction.

The best results of the cocyclotrimerization of 9-Bn-6-alkynylpurine **1aa**−**ca** with various diynes are summarized in Table 1. As for the cocyclotrimerization of **1aa**, only the reaction with dipropargyl ether **2d** catalyzed by Co complex gave a good yield of the product **3aad** (entry 1). In other cases, the yields usually did not exceed 10%. Cocyclotrimerization with the 6-hexynylpurine **1ba** proceeded with diynes generally in good yields of 48−59% under Ni catalysis (entries 2−4). Cocyclotrimerization of dipropargyl ether **2d** proceeded satisfactorily only under Co-catalysis to give the product **3bad** in 55% yield (entry 5). The only exceptions were reactions with 1,6-heptadiyne **2e** and the dipropargylcyanoacetate **2g** that afforded the corresponding products **3bae** and **3bag** in low yields of 11 and 13%, respectively (entries 6 and 7). Reaction with the 6-phenylethynylpurine **1ca** furnished the corresponding 6-arylpurines **3ca*z*** in even better yields in the range of 53−88% (entries 8−12).

Effect of a Catalyst. Nevertheless, these preliminary results sparked deeper interest in the reaction conditions and in finding the scope of the reaction in detail with respect to potential catalysts as well as with respect to structural variations of alkynylpurines. Our initial interest was aimed at finding the most general catalytic system that would give high yields of the corresponding products. The cocyclotrimerization of the 9-tetrahydropyranyl-6-(phenylethynyl)purine **1cb** with the diethyl dipropargylmalonate **2a** was chosen as a model reaction to test the catalytic activity of various transition metal complexes (Scheme 3). Clear from Table 2 is the fact that the most active catalysts were those based on Ni complexes with monodentate and bidentate phosphine ligands. Ni complexes bearing PPh_3, PBu_3, dppm (diphenylphosphinomethane), dppe (diphenylphosphinoethane), and dppp (diphenylphosphinopropane) ligands gave comparable yields (entries 1−3, 5, 6). Only the complex with dppb (diphenylphosphinobutane) gave inferior results. Although the best yield was obtained with $NiBr_2$(dppm) complex, our further experiments showed that the $NiBr_2$-(dppe) complex is of general use for cyclotrimerization of most alkynylpurines and diynes. As far as the solvent used is concerned, the best results were always obtained in MeCN. In this respect, possible additional coordination of MeCN to the central nickel atom during the course of the reaction cannot be ruled out.[21] The use of $CoBr(PPh_3)_3$ gave a negligible yield of the product (entry 7) and thus confirmed its usefulness only in the cocyclotrimerizations with propagyl ether. It has been already mentioned in our preliminary report[10] that $RhCl(PPh_3)_3$ was not catalytically active at all (entry 8). However, in the presence of a stoichiometric amount of the Rh complex, the reaction proceeded well. In addition, the use of the recently reported $[Ir(cod)Cl]_2$/dppe catalytic system (entry 9) for cyclotrimerization of alkynes[22] did not furnish any detectable amount of the product **3cba**. Although speculative, the low activity of the group VIII-based catalysts (Co, Rh, Ir) might be attributed to the formation of complexes with the purine ring heteroatoms that are coordinatively saturated and hence catalytically inactive.[23]

Cocyclotrimerizations of 9-THP-6-Alkynylpurines. Our further aim was to extend this reaction also to 6-alkynylpurines bearing a more easily cleavable protective group at position 9. For that purpose, benzyl protective group was changed to tetrahydropyranyl group because it can be easily removed under mild reaction conditions. Generally, the yields of the corresponding 9-THP-6-arylpurines **3*x*b*z*** obtained from the 9-THP-alkynylpurines **1*x*b** were higher than those obtained with the 9-Bn-6-alkynylpurines **1*x*a**. The results are summarized in Table 3.

Cocyclotrimerizations of the 9-THP-ethynylpurine **1ab** with various diynes **2** usually proceeded to give the corresponding 6-arylpurines in low yields that did not exceed 10%. The only significant improvement was observed in cocyclotrimerization of **1ab** with the dipropargyl ether **2d** catalyzed by Co complex (entry 1). The product **3abd** was obtained in a good yield of 70% at 20 °C. A yield of 73% was obtained when the reaction was carried out at 60 °C. On the other hand, significant increase of the yields of the arylpurines was observed for reactions of the 9-THP-6-hexynylpurine **1bb**. In all cases, the yields were either higher or at least the same as the yields of the corresponding 6-arylpurines obtained from 9-Bn-alkynylpurines **1*x*a**. This is exemplified by the reaction of **1bb** with the dipropargylmalonate **2a** in which a 10% increase in yield was observed (entry 2). For the reaction with the dipropargylacetoacetate **2b** and -acetoacetone **2c** were obtained identical yields of arylpurines **3bbb** and **3bbc** as in the case for the benzyl derivative **1ba** (entries 3 and 4). Once again, a considerable change in the yield of arylpurine was observed in Co-catalyzed cocyclotrimerization with the dipropargyl

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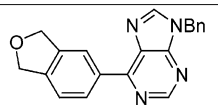
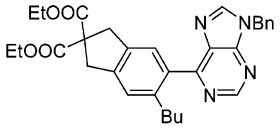
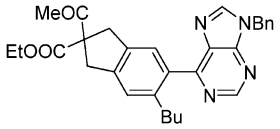
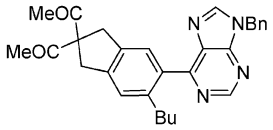
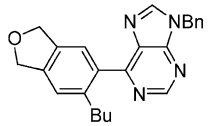
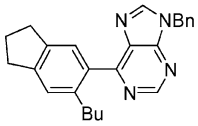
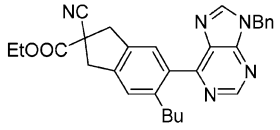
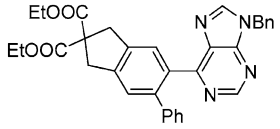
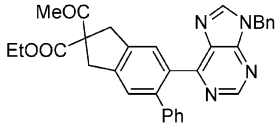
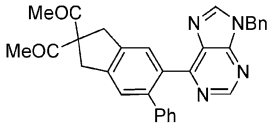
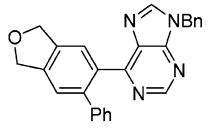
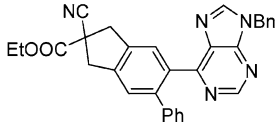
TABLE 1. Catalytic Cocyclotrimerizations with the 9-Bn-6-Alkynylpurines 1x[a]

Entry	Alkynyl purine	Diyne	Catalyst	t (h)[a]	Product		Yield (%)[c]
1	**1aa**	**2d**	$CoBr(PPh_3)_3$	72		(**3aad**)	55
2	**1ba**	**2a**	$NiI_2(PPh_3)_2$/Zn	72		(**3baa**)	48
3		**2b**	$NiBr_2$(dppe)/Zn	72		(**3bab**)	52
4		**2c**	$NiBr_2$(dppe)/Zn	72		(**3bac**)	59
5		**2d**	$CoBr(PPh_3)_3$	24[b]		(**3bad**)	55
6		**2e**	$NiI_2(PPh_3)_2$/Zn	96		(**3bae**)	11
7		**2g**	$NiI_2(PPh_3)_2$/Zn	96		(**3bag**)	13
8	**1ca**	**2a**	$NiBr_2$(dppe)/Zn	20		(**3caa**)	64
9		**2b**	$NiBr_2$(dppe)/Zn	72		(**3cab**)	53
10		**2c**	$NiBr_2$(dppe)/Zn	72		(**3cac**)	68
11		**2d**	$CoBr(PPh_3)_3$	16[b]		(**3cad**)	88
12		**2g**	$NiBr_2$(dppe)/Zn	72		(**3cag**)	62

[a] At 60 °C unless mentioned otherwise. [b] At 20 °C. [c] Isolated yields.

SCHEME 3. Cocyclotrimerization of 1cb with 2a into 3cba

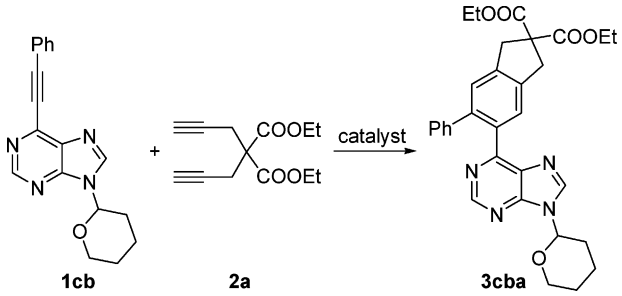


TABLE 2. Catalyst Effect on the Reaction of 1cb with 2a

entry	catalyst[a]	solvent	unreacted alkyne (%)	yield (%)[c]
1	$NiBr_2$(dppm)/Zn	MeCN	14	67
2	$NiBr_2$(dppe)/Zn	MeCN	37	52
3	$NiBr_2$(dppp)/Zn	MeCN	7	64
4	$NiBr_2$(dppb)/Zn	MeCN	55	23
5	$NiBr_2(PPh_3)_2$/Zn	MeCN	0	57
6	$NiBr_2(PBu_3)_2$/Zn	MeCN	0	61
7	$CoBr(PPh_3)_3$[b]	toluene	80	5
8	$RhCl(PPh_3)_3$[b]	toluene	89	7
9	$[Ir(cod)Cl]_2$/dppe[b]	toluene	93	0

[a] Performed with 20 mol % catalyst and 20 °C unless mentioned otherwise. [b] Performed with 10 mol % catalyst. [c] ^{1}H NMR yield.

ether **2d** (entry 5); the arylpurine **3bbd** was obtained in 67% yield. A dramatic effect was observed in cocyclotrimerization of **1bb** with simple 1,6-heptadiyne **2e** where the yield of **3bbe** increased almost 2-fold from 11 to 21% (entry 6). A similar effect was observed in the reaction with **2g**, which afforded the product **3bbg** in 50% yield (entry 7).

A similar trend was observed also for cocyclotrimerizations of the 9-THP-6-phenylethynylpurine **1cb**. The cocyclotrimerization of **1cb** with **2a** gave only a marginally higher yield of the arylpurine **3cba** (entry 8). However, in the reaction with dipropargylacetoacetate **2b** and -acetoacetone **2c**, the yields of the corresponding **3cbb** and **3cbc** were increased by as much as 17 and 9%, respectively (entries 9 and 10). Contrary to the previously observed trend for co-catalyzed cocyclotrimerizations, in the reaction of **1cb** with **2d** was observed a 28% decrease in the yield of the arylpurine **3cbd** (entry 11). The reaction of 1,6-heptadiyne **2e** afforded **3cbe** in 33% yield (entry 12). The cyclotrimerization with the dipropargylcyanoacetate **2g** afforded the product **3cbg** in 64% yield (entry 13).

The compounds **3bbb**, **3bbg**, **3cbb**, and **3cbg** were obtained as inseparable mixtures of diastereoisomers in a 1:1 ratio. Interestingly, in the case of **3bbb**, ^{1}H and ^{13}C NMR spectra of the individual diastereoisomers were indistinguishable from each other. In other cases, there were only slight differences in some of the signals: **3cbb** (^{1}H spectra), **3bbg** (^{13}C spectra), and **3cbg** (^{1}H and ^{13}C spectra).

For comparison of activity of Co and Rh complexes, the reactions in entries 1, 5, and 11 (Table 3) were carried out also in the presence of a catalytic amount of $RhCl(PPh_3)_3$ (10 mol %). In the case of reaction **1ab** with **2d**, its use proved to be totally ineffective: the product **3abd** was not formed. As for the reactions of **1bb** and **1cb** with **2d**, the yields of the corresponding products **3bbd** and **3cbd** were 30 and 34%, respectively. These results clearly indicate the inferiority of the Rh complex in comparison with the Co complex for cocyclotrimerization of dipropargyl ether **2d**.

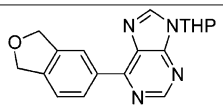
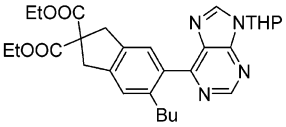
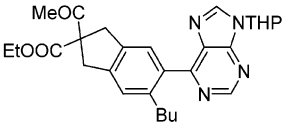
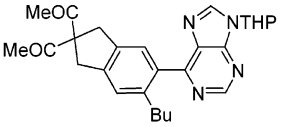
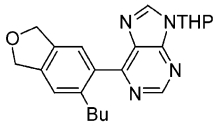
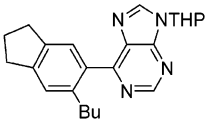
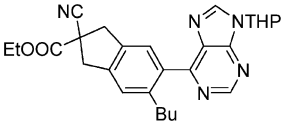
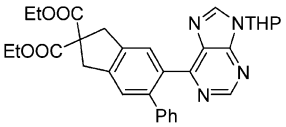
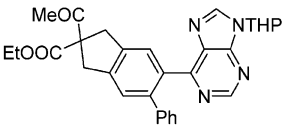
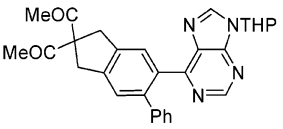
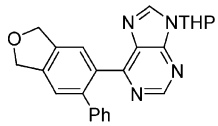
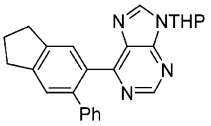
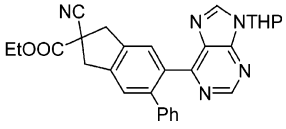
Cyclotrimerizations in the Presence of a Stoichiometric Amount of Ni Complexes. Interestingly, for some combinations the use of any of the catalysts did not result in the formation of benzene derivatives. This prompted us to compare some results with the reactions carried with a stoichiometric amount of a catalyst. For that purpose, $NiI_2(PPh_3)_2$ was chosen because of its low cost. The results are summarized in Table 4. Reactions of the hexynylpurine **1ba** with diynes **2e** and **2g** under stoichiometric conditions gave higher yields of the corresponding products **3bae** (entry 2) and **3bag** (entry 4) than under catalytic conditions. It is notable that the reaction of the ethynylpurine **1aa** with diyne **2a** and the hexynylpurine **1bb** with 1,7-octadiyne **2f** afforded the arylpurines **3aaa** (entry 1, Figure 1) and **3baf** (entry 5, Figure 1) in 9 and 39% yields, respectively. Under catalytic conditions, the formation of neither of these products was detected. The reaction of the hexynylpurine **1ba** with the diyne **2a** gave the arylpurine **3baa** in a yield (52%) comparable to that of the catalytic reaction (entry 3). The reaction of the hexynylpurine **1bb** with the diyne **2g** and phenylethynylpurines **1ca** and **1cb** with diynes **2a** and **2g** gave arylpurines **3bbg** (26%, entry 6), **3caa** (22%, entry 7), **3cag** (15%, entry 8), and **3cbg** (12%, entry 9) in inferior yields in comparison with the catalytic reactions.

Deprotection of 9-THP-6-Arylpurines. In the next step, the obtained 9-THP-6-arylpurines **3*xbz*** were subjected to deprotection to obtain the free purine bases **3*xcz***. For the deprotection, a mild method, Dowex 50 (H^+ form) in refluxing EtOH,[24] was chosen with respect to possible side-reactions caused by the presence of the ester or keto groups in the starting molecules. The results are summarized in Table 5. Generally, the deprotection proceeded uneventfully in all cases to give expected free purine bases **3*xcz***. In the cases of the isobenzofuranyl-**3abd** and dicarboxyethylindanylpurine **3bba**, the yields of the corresponding free bases **3acd** and **3bca** were as high as 91 and 89%, respectively (entries 1 and 2). For others, the deprotection afforded the products **3bcb**, **3cca**, and **3ccb** (entries 3−5) in good yields in the range of 65−76%. Recrystallization of **3acd** from a mixture of $DMSO/H_2O$ afforded suitable crystals for X-ray analysis that unequivocally confirmed its structure (see Supporting Information).

Biological Activity. Preliminary in vitro cytostatic activity tests of some representative examples of each class of the title compounds (9-benzyl-6-arylpurines **3baa**, **3bab**, **3bae**, **3bag**, **3caa**, **3cab**, and **3cag**; 9-THP-6-arylpurines **3abd**, **3bba**, **3bbb**, **3bbg**, **3cba**, **3cbb**, and **3cbg**; free purine bases **3acd**, **3bca**, **3bcb**, **3cca**, and **3ccb**) were performed using the following cell cultures: mouse leukemia L1210 cells (ATCC CCL 219); human promyelocytic leukemia HL60 cells (ATCC CCL 240); human cervix carcinoma HeLa S3 cells (ATCC CCL 2.2); and human T lymphoblastoid CCRF-CEM cell line (ATCC

(24) Hocek, M.; Holý, A. *Collect. Czech. Chem. Commun.* **1995**, *60*, 1386−1389.

TABLE 3. Catalytic Cocyclotrimerizations with the 9-THP-6-Alkynylpurines 1*x*b

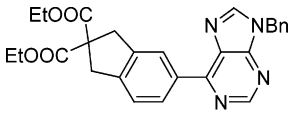
Entry	Alkynyl purine	Diyne	Catalyst	t (h)[a]	Product		Yield (%)[c]
1	**1ab**	**2d**	$CoBr(PPh_3)_3$	5[b]		(**3abd**)	70
2	**1bb**	**2a**	$NiBr_2$(dppe)/Zn	72		(**3bba**)	58
3		**2b**	$NiBr_2$(dppe)/Zn	72		(**3bbb**)	52
4		**2c**	$NiBr_2$(dppe)/Zn	72[b]		(**3bbc**)	59
5		**2d**	$CoBr(PPh_3)_3$	24[b]		(**3bbd**)	67
6		**2e**	$NiBr_2$(dppe)/Zn	72		(**3bbe**)	21
7		**2g**	$NiBr_2$(dppe)/Zn	72		(**3bbg**)	50
8	**1cb**	**2a**	$NiBr_2$(dppe)/Zn	72[b]		(**3cba**)	67
9		**2b**	$NiBr_2$(dppe)/Zn	72		(**3cbb**)	70
10		**2c**	$NiBr_2$(dppe)/Zn	72[b]		(**3cbc**)	77
11		**2d**	$CoBr(PPh_3)_3$	24[b]		(**3cbd**)	60
12		**2e**	$NiBr_2$(dppe)/Zn	72		(**3cbe**)	33
13		**2g**	$NiBr_2$(dppe)/Zn	72		(**3cbg**)	64

[a] At 60 °C unless mentioned otherwise. [b] At 20 °C. [c] Isolated yields.

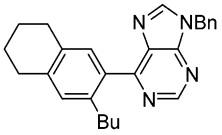
TABLE 4. Cocyclotrimerization of 1 with 2 in the Presence of a Stoichiometric Amount of $NiI_2(PPh_3)_2$

entry	alkynylpurine	diyne	*t* (h)[a]	product	yield (%)[b]
1	**1aa**	**2a**	72	**3aaa**	9
2	**1ba**	**2e**	48	**3bae**	29
3	**1ba**	**2a**	48	**3baa**	52
4	**1ba**	**2g**	24	**3bag**	33
5	**1ba**	**2f**	24	**3baf**	39
6	**1bb**	**2g**	24	**3bbg**	26
7	**1ca**	**2a**	48	**3caa**	22
8	**1ca**	**2g**	24	**3cag**	15
9	**1cb**	**2g**	24	**3cbg**	12

[a] At 60 °C. [b] Isolated yields.



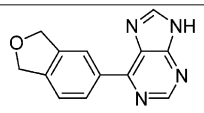
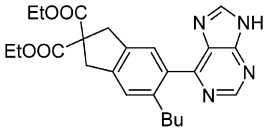
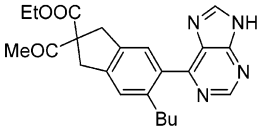
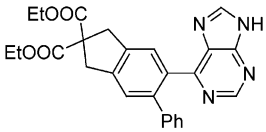
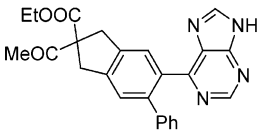
3aaa



3baf

FIGURE 1. Structures for **3aaa** and **3baf**.

TABLE 5. Deprotection of the 9-THP-6-Arylpurines 3*xbz* to the Free Purine Bases 3*xcz*

Entry	3*xbz*	6-arylpurine		Yield (%)[a]
1	**3abd**		(**3acd**)	91
2	**3bba**		(**3bca**)	89
3	**3bbb**		(**3bcb**)	76
4	**3cba**		(**3cca**)	65
5	**3cbb**		(**3ccb**)	67

[a] Isolated yield.

CCL 119).[25] Some of the compounds showed considerable activity (Table 6), in particular against HL60 and CCRF-CEM cell lines. In general, the 9-benzyl derivatives **3*xaz*** were more active than 9-THP derivatives **3*xbz***, while the free purine bases **3*xcz*** were entirely inactive. Compound

TABLE 6. Cytostatic Activity of Selected 6-Arylpurines 3

	IC_{50} (μmol L^{-1})[a]			
compound	L1210	HL60	HeLa S3	CCRF−CEM
3baa	7.4	7.0	NA	11.6
3bae	NA	13.0	NA	NA
3bag	2.2	1.0	2.5	0.93
3caa	NA	9.4	2.5	25.0
3bab	NA	9.5	NA	9.0
3cag	NA	6.7	NA	8.8
3bba	16.0	13.5	NA	18.3
3bbg	NA	NA	NA	14.8
3cbg	NA	NA	NA	15.0
FUDR[b]	0.012	0.012	NA	0.017

[a] Concentration of a compound needed to reduce population growth of organism by 50% in vitro. NA = not active, inhibition of the cell growth at $c = 10$ μmol L^{-1} was lower than 20%. [b] 1-(β-D-2-Deoxy-*erythro*-pentofuranosyl)-5-fluorouracil.

3bag bearing a combination of cyano, ethoxycarbonyl, and butyl groups on the dihydroindan moiety was the most active in this series. Though the activities in the micromolar range, about 2 orders of magnitude lower compared to standard cytostatic 1-(β-D-2-deoxy-*erythro*-pentofuranosyl)-5-fluorouracil (FUDR), are probably below the therapeutically useful level, this novel type of compound definitely represents a new structural lead in the search of antiproliferative drugs. Further investigations will focus on extension of the series of this promising class of compounds for SAR study and on the use of some of the hydrophobic purines as artificial nucleobase surrogates in modified nucleic acids.

Conclusion

In conclusion, we have shown that [2 + 2 + 2]-cocyclotrimerization with purine systems is a synthetically useful and efficient method that allows the preparation of highly substituted 6-arylpurines (in particular purines bearing benzoisofuranyl and indanyl moieties) that would not be easily accessible by standard cross-coupling reactions. Moreover screening of different cyclotrimerization catalysts showed that Ni−phosphine complexes are superior in catalytic activity and proved to be the catalysts of choice when cyclotrimerization of nitrogen-rich alkynes is concerned. Although the true nature of this effect is not clarified yet, the results indicate that proper choice of the protecting group (tetrahydropyranyl-THP) in position 9 may have beneficial influence on the course of the reaction. In addition, the presented results show that Ni−phosphine complexes are catalysts of choice for cyclotrimerization of alkynes bearing a heterocyclic moiety.

Experimental Section

General Procedure for Catalytic Cyclotrimerization of 6-Alkynylpurines with Diynes: Ni-Catalyzed Reactions. To a solution of 6-alkynylpurine **1*xa*** or **1*xb*** (0.1 mmol), a diyne **2** (0.1 mmol), and a Ni complex (0.02 mmol) in MeCN (2 mL) under Ar was added Zn powder (5 mg, 0.08 mmol). The reaction mixture was initially stirred at 20 °C; if the reaction did not proceed or the rate was too slow, the content was heated at 60 °C. Then, the reaction mixture was filtered

(25) For experimental details of the assays, see ref 3a.

through a plug of wool and concentrated under reduced pressure. Further subjection to column chromatography afforded the product. **Co- or Rh-Catalyzed Reactions.** A solution of 6-alkynylpurine **1*x*a** or **1*x*b** (0.1 mmol), a diyne **2** (0.1 mmol), and a Co or Rh complex (0.02 mmol) in toluene (2 mL) under Ar was initially stirred at 20 °C; if the reaction did not proceed or the rate was too slow, the content was heated at 60 °C. Further steps followed the previously mentioned procedure.

6-(1,3-Dihydroisobenzofuran-5-yl)-9-(tetrahydropyran-2-yl)-9*H*-purine (3abd). The reaction was catalyzed by $CoBr(PPh_3)_3$. Column chromatography on silica gel (1/1 hexane/EtOAc) afforded 46 mg (70%) of a white solid: mp 153−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64−1.71 (m, 1H), 1.71−1.89 (m, 2H), 2.05−2.15 (m, 2H), 2.15−2.22 (m, 1H), 3.82 (dt, J = 11.7, 2.7 Hz, 1H), 4.18−4.24 (m, 1H), 5.19 (s, 2H), 5.23 (s, 2H), 5.85 (dd, J = 10.2, 2.6 Hz, 1H), 7.43 (d, J = 8 Hz, 1H), 8.24 (s, 1H), 8.69 (s, 1H), 8.76 (d, J = 8 Hz, 1H), 9.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 24.8, 31.8, 68.8, 73.5, 73.5, 81.9, 121.1, 122.3, 129.3, 130.9, 135.0, 139.8, 142.0, 142.2, 151.7, 152.3, 154.5; IR ($CHCl_3$) ν 3017, 1585, 1571, 1222, 1217, 1207, 1200, 1086, 1046 cm^{-1}; EI-MS *m/z* (% relative intensity) 322 (M^+, 30), 294 (15), 239 (43), 210 (100), 85 (62), 41 (44); HR-MS cacld for $C_{18}H_{18}N_4O_2$ 322.1430, found 322.1421; R_f (EtOAc) = 0.35.

6-(6-Butyl-2,2-di(carboxyethyl)indan-5-yl)-9-(tetrahydropyran-2-yl)-9*H*-purine (3bba). The reaction was catalyzed by $NiBr_2$(dppe)/Zn. Column chromatography on silica gel (3/2 hexane/EtOAc) afforded 60 mg (58%) of pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.71 (t, J = 7.3 Hz, 3H), 1.09−1.18 (m, 2H), 1.26 (t, J = 7.1 Hz, 6H), 1.34−1.42 (m, 2H), 1.66−1.71 (m, 1H), 1.73−1.90 (m, 2H), 2.04−2.23 (m, 3H), 2.66−2.78 (m, 2H), 3.63 (s, 2H), 3.64 (s, 2H), 3.83 (dt, J = 11.7, 2.7 Hz, 1H), 4.40 (q, J = 7.2 Hz, 4H), 4.38−4.42 (m, 1H), 5.87 (dd, J = 10.1, 2.9 Hz, 1H), 7.22 (s, 1H), 7.39 (s, 1H), 8.30 (s, 1H), 9.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 13.9 (2C), 22.3, 22.7, 24.8, 31.6, 32.78, 33.4, 40.0, 40.4, 60.5, 61.7 (2C), 68.8, 81.9, 125.7, 126.1, 132.2, 133.3, 137.4, 140.8, 141.9, 142.3, 150.8, 152.1, 159.5, 171.5 (2C); IR ($CHCl_3$) ν 3017, 2986, 2961, 1731, 1589, 1297, 1277, 1251, 1224, 1212, 1207, 1197, 1190, 1086, 1059, 1046, 909 cm^{-1}; EI-MS *m/z* (% relative intensity) 520 (M^+, 3), 435 (100), 407 (22), 83 (12); HR-MS cacld for $C_{29}H_{36}N_4O_5$ 520.2686, found 520.2700; R_f (1/3 hexane/EtOAc) = 0.41.

6-(6-Butyl-2-acetyl-2-(carboxyethyl)indan-5-yl)-9-(tetrahydropyran-2-yl)-9*H*-purine (3bbb). The reaction was catalyzed by $NiBr_2$(dppe)/Zn. Column chromatography on silica gel (3/2 hexane/EtOAc) afforded 51 mg (52%) of a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.72 (t, J = 7.3 Hz, 3H), 1.10−1.18 (m, 2H), 1.27 (t, J = 7.2 Hz, 3H), 1.35−1.43 (m, 2H), 1.66−1.71 (m, 1H), 1.72−1.90 (m, 2H), 2.04−2.23 (m, 3H), 2.24 (s, 3H), 2.68−2.79 (m, 2H), 3.51−3.65 (m, 4H), 3.83 (dt, J = 11.8, 2.7 Hz, 1H), 4.18−4.26 (m, 1H), 4.22 (q, J = 7.1 Hz, 2H), 5.86 (dd, J = 10, 3 Hz, 1H), 7.21 (s, 1H), 7.40 (s, 1H), 8.28 (s, 1H), 9.02 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 14.0, 22.4, 22.77, 24.8, 26.1, 31.7, 32.9, 33.5, 38.7, 38.9, 61.8, 67.0, 68.8, 81.9, 125.8, 126.3, 132.3, 133.6, 137.3, 141.0, 141.8, 142.2, 150.9, 152.2, 159.5, 172.2, 202.7; IR ($CHCl_3$) ν 3017, 2960, 1715, 1589, 1240, 1222, 1218, 1212, 1209, 1199, 1188, 1086, 1045, 909 cm^{-1}; EI-MS *m/z* (% relative intensity) 490 (M^+, 3), 405 (100), 377 (24), 203 (17); HR-MS cacld for $C_{28}H_{34}N_4O_4$ 490.2580, found 490.2548; R_f (1/3 hexane/EtOAc) = 0.35.

6-(6-Butyl-2,2-diacetylindan-5-yl)-9-(tetrahydropyran-2-yl)-9*H*-purine (3bbc). The reaction was catalyzed by $NiBr_2$(dppe)/Zn. Column chromatography on silica gel (1/1 hexane/EtOAc) afforded 54 mg (59%) of a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.72 (t, J = 7.3 Hz, 3H), 1.09−1.19 (m, 2H), 1.34−1.43 (m, 2H), 1.65−1.72 (m, 1H), 1.72−1.90 (m, 2H), 2.06−2.24 (m, 3H), 2,19 (s, 6H), 2.66−2.78 (m, 2H), 3.55 (s, 4H), 3.83 (dt, J = 11.7, 2.7 Hz, 1H), 4.18−4.24 (m, 1H), 5.87 (dd, J = 10, 2.9 Hz, 1H), 7.23 (s, 1H), 7.41 (s, 1H), 8.30 (s, 1H), 9.02 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 22.3, 22.7, 24.8, 26.5 (2C), 31.6, 32.8, 33.4, 37.3, 37.5, 68.8, 74.7, 81.9, 125.9, 126.4, 132.2, 133.6, 137.1, 141.1, 141.6, 142.3, 150.8, 152.2, 159.3, 204.9 (2C); IR ($CHCl_3$) ν 3036, 3023, 3016, 2960, 2935, 2865, 1702, 1589, 1502, 1456, 1444, 1410, 1379, 1359, 1330, 1220, 1214, 1208, 1187, 1165, 1145, 1086, 1059, 1045, 909 cm^{-1}; EI-MS *m/z* (% relative intensity) 460 (M^+, 2), 375 (88), 347 (41), 333 (100), 305 (33), 291 (17), 84 (52); HR-MS cacld for $C_{27}H_{32}N_4O_3$ 460.2474, found 460.2483; R_f (EtOAc) = 0.38.

6-(6-Butyl-1,3-dihydroisobenzofuran-5-yl)-9-(tetrahydropyran-2-yl)-9*H*-purine (3bbd). The reaction was catalyzed by $CoBr(PPh_3)_3$. Column chromatography on silica gel (3/2 hexane/EtOAc) afforded 51 mg (67%) of a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (t, J = 7.2 Hz, 3H), 1.11−1.22 (m, 2H), 1.38−1.47 (m, 2H), 1.64−1.72 (m, 1H), 1.72−1.90 (m, 2H), 2.06−2.16 (m, 2H), 2.16−2.26 (m, 1H), 2.73−2.86 (m, 2H), 3.83 (dt, J = 11.7, 2.6 Hz, 1H), 4.18−4.24 (m, 1H), 5.15 (s, 4H), 5.87 (dd, J = 10.4, 2.8 Hz, 1H), 7.26 (s, 1H), 7.47 (s, 1H), 8.30 (s, 1H), 9.05 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 22.3, 22.7, 24.8, 31.7, 32.9, 33.5, 68.9, 73.4, 73.4, 82.1, 122.5, 123.2, 128.3, 132.2, 136.7, 141.2, 141.6, 142.8, 151.1, 151.8, 158.8; IR ($CHCl_3$) ν 2957, 1588, 1332, 1231 cm^{-1}; EI-MS *m/z* (% relative intensity) 378 (M^+, 5), 293 (100), 265 (66), 84 (57); HR-MS cacld for $C_{22}H_{26}N_4O_2$ 378.2056, found 378.2072; R_f (EtOAc) = 0.27.

6-(6-Butylindan-5-yl)-9-(tetrahydropyran-2-yl)-9*H*-purine (3bbe). The reaction was catalyzed by $NiBr_2$(dppe)/Zn. Column chromatography on silica gel (5/2 hexane/EtOAc) afforded 16 mg (21%) of a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.71 (t, J = 7.2 Hz, 3H), 1.08−1.20 (m, 2H), 1.35−1.44 (m, 2H), 1.66−1.73 (m, 1H), 1.73−1.91 (m, 2H), 2.04−2.18 (m, 2H), 2.09 (p, J = 7.6 Hz, 2H), 2.18−2.26 (m, 1H), 2.65−2.78 (m, 2H), 2.92 (t, J = 7.0 Hz, 2H), 2.94 (t, J = 7.0 Hz, 2H), 3.84 (dt, J = 11.8, 2.7 Hz, 1H), 4.19−4.25 (m, 1H), 5.88 (dd, J = 10.4, 2.8 Hz, 1H), 7.24 (s, 1H), 7.42 (s, 1H), 8.33 (s, 1H), 9.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 22.4, 22.8, 24.8, 25.5, 31.7, 32.4, 32.8, 32.9, 33.7, 68.9, 82.1, 126.1, 126.3, 131.2, 132.2, 139.9, 141.8, 142.7, 146.8, 151.0, 151.7, 159.5; IR ($CHCl_3$) ν 3023, 2960, 2866, 2294, 2257, 1589, 1455, 1442, 1374, 1331, 1227, 1221, 1214, 1086, 1045 cm^{-1}; EI-MS *m/z* (% relative intensity) 376 (M^+, 6), 291 (100), 263 (62), 248 (22), 85 (16); HR-MS cacld for $C_{23}H_{28}N_4O$ 376.2263, found 376.2272; R_f (1/3 hexane/EtOAc) = 0.49.

6-(6-Butyl-2-cyano-2-(carboxyethyl)indan-5-yl)-9-(tetrahydropyran-2-yl)-9*H*-purine (3bbg). The reaction was catalyzed by $NiBr_2$(dppe)/Zn. Column chromatography on silica gel (2/1 toluene/EtOAc) afforded 47 mg (50%) of a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (t, J = 7.2 Hz, 3H), 1.10−1.20 (m, 2H), 1.35 (t, J = 7.2 Hz, 3H), 1.36−1.46 (m, 2H), 1.64−1.72 (m, 1H), 1.72−1.90 (m, 2H), 2.06−2.24 (m, 3H), 2.70−2.80 (m, 2H), 3.61 (d, J = 16.5 Hz, 1H), 3.62 (d, J = 16.3 Hz, 1H), 3.73 (d, J = 13.4 Hz, 1H), 3.77 (d, J = 16.3 Hz, 1H), 3.84 (dt, J = 11.5, 2.5 Hz, 1H), 4.18−4.25 (m, 1H), 4.31 (q, J = 7.2 Hz, 2H), 5.87 (dd, J = 10.1, 2.9 Hz, 1H), 7.27 (s, 1H), 7.45 (s, 1H), 8.30 (s, 1H), 9.03 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.70, 13.9, 22.4, 22.8, 24.8, 31.7, 32.9, 33.4, 42.9, 43.0, 47.40 + 47.43, 63.2, 68.9, 82.0, 120.5, 126.0, 126.5, 132.2, 134.3, 135.6, 140.0, 142.0, 142.4, 151.0, 152.3, 158.9, 168.4; IR ($CHCl_3$) ν 2955, 2860, 2247, 1740, 1590, 1498, 1454, 1328, 1219, 1083, 1045, 906 cm^{-1}; EI-MS *m/z* (% relative intensity) 473 (M^+, 2), 388 (100), 360 (50), 286 (16), 134 (26); R_f (1/3 toluene/EtOAc) = 0.47.

6-[6-Phenyl-2,2-di(carboxyethyl)indan-5-yl]-9-(tetrahydropyran-2-yl)-9*H*-purin (3cba). The reaction was catalyzed by $NiBr_2$(dppe)/Zn. Column chromatography on silica gel (3/2 hexane/EtOAc) afforded 72 mg (67%) of a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 6H), 1.60−1,68 (m, 1H), 1.68−1.84 (m, 2H), 2.00−2.14 (m, 3H), 3.70 (s, 2H), 3.72 (s, 2H), 3.78 (dt, J = 11.6, 2.7 Hz, 1H), 4.14−4.26 (m, 1H), 4.23 (q, J = 7.0 Hz, 4H), 5.76 (dd, J = 9.7, 2.8 Hz, 1H), 7.08−7.14 (m, 5H), 7.38 (s, 1H), 7.60 (s, 1H), 8.12 (s, 1H), 8.81 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (2C), 22.7, 24.8,

31.5, 40.2, 40.4, 60.6, 61.7 (2C), 68.7, 81.9, 126.3, 126.6, 126.6, 127.7 (2C), 129.1 (2C), 132.3, 133.3, 139.2, 141.1, 141.3, 141.9, 142.2, 150.7, 152.1, 159.2, 171.4 (2C); IR ($CHCl_3$) ν 3025, 3017, 2987, 1731, 1590, 1446, 1329, 1298, 1270, 1248, 1225, 1213, 1207, 1191, 1163, 1086, 1058, 1046, 907 cm^{-1}; EI-MS *m/z* (% relative intensity) 540 (M^+, 6), 455 (26), 221 (64), 149 (17), 84 (67); HR-MS cacld for $C_{31}H_{32}N_4O_5$ 540.2373, found 540.2387; R_f (1/2 hexane/EtOAc) = 0.40.

6-(6-Phenyl-2-acetyl-2-(carboxyethyl)indan-5-yl)-9-(tetrahydropyran-2-yl)-9*H*-purine (3cbb). The reaction was catalyzed by $NiBr_2$(dppe)/Zn. Column chromatography on silica gel (1/1 hexan/EtOAc) afforded 72 mg (70%) of a pale yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, J = 7.2 Hz, 3H), 1.61−1.68 (m, 1H), 1.68−1.84 (m, 2H), 1.99−2.15 (m, 3H), 2.27 (s, 3H), 3.58−3.72 (m, 4H), 3.78 (dt, J = 11.7, 2.8 Hz, 1H), 4.13−4.20 (m, 1H), 4.24 (q, J = 7.1 Hz, 2H), 5.76 (dd, J = 9.8, 2.6 Hz, 1H), 7.08−7.14 (m, 5H), 7.37 (s, 1H), 7.60 (s, 1H), 8.11 (s, 0.5H), 8.12 (s, 0.5H), 8.81 (s, 0.5H), 8.81 (s, 0.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.7, 24.8, 26.10, 31.5, 38.7, 38.9, 61.9, 67.1, 68.7, 81.8, 126.4, 126.6, 126.7, 127.7 (2C), 129.1 (2C), 132.3, 133.4, 139.0, 141.2 (2C), 142.0, 142.1, 150.7, 152.1, 159.2, 172.1, 202.4; IR ($CHCl_3$) ν 1715, 1590, 1238, 1223, 1218, 1213, 1209, 1199, 908 cm^{-1}; EI-MS *m/z* (% relative intensity) 510 (M^+, 14), 425 (53), 383 (38), 353 (17), 57 (100); HR-MS calcd for $C_{30}H_{30}N_4O_4$ 510.2267, found 510.2243; R_f (EtOAc) = 0.37.

6-(6-Phenyl-2,2-diacetylindan-5-yl)-9-(tetrahydropyran-2-yl)-9*H*-purine (3cbc). The reaction was catalyzed by $NiBr_2$-(dppe)/Zn. Column chromatography on silica gel (2/5 hexane/EtOAc) afforded 74 mg (77%) of colorless crystals: mp 157−159 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.60−1.68 (m, 1H), 1.68−1.85 (m, 2H), 1.99−2.18 (m, 3H), 2.21 (s, 6H), 3.62 (s, 2H), 3.63 (s, 2H), 3.78 (dt, J = 11.6, 2.6 Hz, 1H), 4.13−4.19 (m, 1H), 5.76 (dd, J = 9.9, 2.7 Hz, 1H), 7.08−7.12 (m, 5H), 7.38 (s, 1H), 7.61 (s, 1H), 8.12 (s, 1H), 8.81 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 24.7, 26.5 (2C), 31.52 37.3, 37.5, 68.7, 74.9, 81.8, 126.4, 126.8, 126.9, 127.7 (2C), 129.1 (2C), 132.2, 133.5, 138.9, 141.1, 141.3, 141.9, 142.0, 150.7, 152.1, 159.0, 204.5 (2C); IR ($CHCl_3$) ν 3016, 2988, 1702, 1590, 1359, 1328, 1218, 1206, 1087, 1045 cm^{-1}; EI-MS *m/z* (% relative intensity) 480 (M^+, 5), 353 (37), 277 (98), 84 (69), 55 (100); HR-MS cacld for $C_{29}H_{28}N_4O_3$ 480.2161, found 480.2191; R_f (EtOAc) = 0.35.

6-(6-Phenyl-1,3-dihydroisobenzofuran-5-yl)-9-(tetrahydropyran-2-yl)-9*H*-purine (3cbd). The reaction was catalyzed by $CoBr(PPh_3)_3$. Column chromatography on silica gel (1/2 hexane/EtOAc) afforded 48 mg (60%) of a pale yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.61−1.68 (m, 1H), 1.68−1.86 (m, 2H), 2.00−2.17 (m, 3H), 3.78 (dt, J = 11.6, 2.8 Hz, 1H), 4.14−4.20 (m, 1H), 5.22 (s, 4H), 5.77 (dd, J = 10, 2.8 Hz, 1H), 7.10−7.18 (m, 5H), 7.41 (s, 1H), 7.65 (s, 1H), 8.15 (s, 1H), 8.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 24.7, 31.5, 68.8, 73.4, 73.4, 81.8, 123.3, 123.5, 126.6, 127.8 (2C), 129.1 (2C), 132.3, 133.6, 138.3, 141.0, 141.1, 141.6, 142.2, 150.7, 152.1, 158.9; IR ($CHCl_3$) ν 2982, 1590, 1332, 1222 cm^{-1}; EI-MS *m/z* (% relative intensity) 398 (M^+, 18), 313 (100), 277 (65), 85 (19); HR-MS cacld for $C_{24}H_{22}N_4O_2$ 398.1743, found 398.1760; R_f (EtOAc) = 0.21.

6-(6-Phenylindan-5-yl)-9-(tetrahydropyran-2-yl)-9*H*-purine (3cbe). The reaction was catalyzed by $NiBr_2$(dppe)/Zn. Column chromatography on silica gel (3/2 hexane/EtOAc) afforded 26 mg (33%) of a pale yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.61−1.68 (m, 1H), 1.68−1.85 (m, 2H), 2.00−2.19 (m, 3H), 2.15 (p, J = 7.2 Hz, 2H), 3.01 (t, J = 7.3 Hz, 4H), 3.79 (dt, J = 11.7, 2.8 Hz, 1H), 4.14−4.20 (m, 1H), 5.77 (dd, J = 9.8, 3.2 Hz, 1H), 7.06−7.16 (m, 5H), 7.39 (s, 1H), 7.62 (s, 1H), 8.13 (s, 1H), 8.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 24.8, 25.6, 31.6, 32.6, 32.9, 68.8, 81.8, 126.1, 126.8, 126.8, 127.7 (2C), 129.2 (2C), 132.3, 132.4, 140.1, 141.7, 141.8, 143.4, 146.4, 150.6, 152.1, 159.9; IR ($CHCl_3$) ν 3014, 2956, 2865, 1589, 1496, 1455, 1409, 1328, 1218, 1086, 1045, 908 cm^{-1}; EI-MS *m/z* (% relative intensity) 396 (M^+, 16), 311 (100), 221 (22), 85 (17); HR-MS cacld for $C_{25}H_{24}N_4O$ 396.1950, found 396.1960; R_f (1/3 hexane/EtOAc) = 0.33.

6-(6-Phenyl-2-cyano-2-(carboxyethyl)indan-5-yl)-9-(tetrahydropyran-2-yl)-9*H*-purine (3cbg). The reaction was catalyzed by $NiBr_2$(dppe)/Zn. Column chromatography on silica gel (2/1 toluene/EtOAc) afforded 63 mg (64%) of a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, J = 7.2 Hz, 3H), 1.60−1.69 (m, 1H), 1.69−1.86 (m, 2H), 1.98−2.16 (m, 3H), 3.68 (d, J = 16.4 Hz, 1H), 3.70 (d, J = 16.4 Hz, 1H), 3.72−3.82 (m, 1H), 3.82 (d, J = 16.4 Hz, 1H), 3.84 (d, J = 16.4 Hz, 1H), 4.16−4.22 (m, 1H), 4.33 (q, J = 7.2 Hz, 2H), 5.77 (dd, J = 9.6, 2.4 Hz, 1H), 7.10−7.14 (m, 5H), 7.42 (s, 1H), 7.65 (s, 1H), 8.13 (s, 0.5H), 8.14 (s, 0.5H), 8.81 (s, 0.5H), 8.82 (s, 0.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.8, 24.8, 31.6, 42.9, 43.0, 47.47 + 47.50, 63.3, 68.8, 81.9, 120.4, 126.7, 126.9, 127.0, 127.9 (2C), 129.1 (2C), 132.3, 134.1, 137.3, 140.3, 140.8, 142.1, 142.2, 150.8, 152.2, 158.6, 168.2; IR ($CHCl_3$) ν 2924, 2860, 2247, 1743, 1590, 1491, 1444, 1331, 1236, 1086, 1042, 906 cm^{-1}; EI-MS *m/z* (% relative intensity) 493 (M^+, 1), 492 ($M^+ - 1$, 2), 407 (95), 349 (100), 321 (70), 305 (84), 292 (36); R_f (1/3 toluene/EtOAc) = 0.44.

General Produre for Deprotection of 9-THP-6-Arylpurines to 6-Arylpurines 3*xcz*. A reaction mixture composed of 9-THP-6-arylpurine (0.3 mmol) and Dowex D-50 (50 mg) in EtOH (20 mL) was refluxed for 1 h or until the starting material was consumed (followed by TLC). The reaction mixture was filtered through frite, and the residuum was washed with hot EtOH (3 × 10 mL); finally, the combined organic fractions were concentrated under reduced pressure.

6-(1,3-Dihydroisobenzofuran-5-yl)-9*H*-purine (3acd). The deprotection of **3abd** (97 mg, 0.3 mmol) afforded 65 mg (91%) of the title compound as a white solid: mp 270−272 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 5.09 (s, 2H), 5.12 (s, 2H), 7.52 (d, J = 7.9 Hz, 1H), 8.63 (s, 1H), 8.81 (s, 1H), 8.83 (d, J = 8.5 Hz, 1H), 8.93 (s, 1H), 13.65 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 72.5 (2C), 121.3, 121.7, 128.6, 129.8, 135.00, 139.6, 142.0, 144.7, 151.8, 152.0, 153.4; IR (KBr) ν 2822, 1571, 1441, 1405, 1320 cm^{-1}; EI-MS *m/z* (% relative intensity) 238 (M^+, 47), 210 (100), 182 (8), 155 (13), 128 (11); HR-MS cacld for $C_{13}H_{10}N_4O$ 238.0855, found 238.0850.

6-(6-Butyl-2,2-di(carboxyethyl)indan-5-yl)-9*H*-purine (3bca). The deprotection of **3bba** (80 mg, 0.15 mmol) afforded 60 mg (89%) of the title compound as a colorless liquid: ^1H NMR (400 MHz, DMSO-d_6) δ 0.63 (t, J = 7.2 Hz, 3H), 1.00−1.10 (m, 2H), 1.19 (t, J = 7.2 Hz, 6H), 1.22−1.32 (m, 2H), 2.60−2.72 (m, 2H), 3.52 (s, 2H), 3.56 (s, 2H), 4.18 (q, J = 7.2 Hz, 4H), 7.24 (s, 1H), 7.41 (s, 1H), 8.53 (s, 1H), 8.91 (s, 1H), 13.57 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.4, 13.8 (2C), 21.7, 32.3, 33.0, 59.7, 61.5 (2C), 125.4, 126.5, 131.2, 134.0, 136.9, 140.4, 141.1, 144.5, 151.5, 152.5, 157.4, 170.9 (2C); IR ($CHCl_3$) 3440, 2984, 1728, 1595, 1251 cm^{-1}; EI-MS *m/z* (% relative intensity) 436 (M^+, 12), 407 (9), 261 (4), 31 (100); HR-MS cacld for $C_{24}H_{28}N_4O_4$ 436.2111, found 436.2101.

6-(6-Butyl-2-acetyl-2-(carboxyethyl)indan-5-yl)-9*H*-purine (3bcb). The deprotection of **3bbb** (100 mg, 0.2 mmol) afforded 63 mg (76%) of the title compound as a colorless liquid: ^1H NMR (400 MHz, DMSO-d_6) δ 0.60 (t, J = 7.2 Hz, 3H), 0.98−1.11 (m, 2H), 1.20 (t, J = 7.2 Hz, 3H), 1.20−1.32 (m, 2H), 2.23 (s, 3H), 2.60−2.72 (m, 2H), 3.42−3.58 (m, 4H), 4.18 (q, J = 7.2 Hz, 2H), 7.23 (s, 1H), 7.40 (s, 1H), 8.53 (s, 1H), 8.92 (s, 1H), 13.55 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.4, 13.8, 21.7, 26.1, 32.1, 33.0, 38.0, 38.3, 61.5, 66.3, 125.5, 126.3, 133.8, 137.2, 140.2, 141.4, 151.5, 171.8, 202.6; IR ($CHCl_3$) 3439, 2985, 1713, 1587, 1236 cm^{-1}; EI-MS *m/z* (% relative intensity) 406 (M^+, 77), 377 (98), 363 (38), 245 (29), 55 (100); HR-MS cacld for $C_{23}H_{26}N_4O_3$ 406.2005, found 406.2010.

6-(6-Phenyl-2,2-di(carboxyethyl)indan-5-yl)-9*H*-purine (3cca). The deprotection of **3cba** (100 mg, 0.18 mmol) afforded 55 mg (65%) of the title compound as a colorless liquid: ^1H NMR (400 MHz, DMSO-d_6) δ 1.21 (t, J = 7.2 Hz, 6H), 3.62 (s, 2H), 3.65 (s, 2H), 4.19 (q, J = 7.2 Hz, 4H), 6.99−7.03 (m, 2H), 7.07−7.12 (m, 3H), 7.41 (s, 1H), 7.54 (s, 1H), 8.39

(s, 1H), 8.77 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.8, 59.7, 61.5, 126.1, 126.4, 126.5, 127.7 (2C), 128.7 (2C), 133.5, 138.9, 140.2, 140.5, 141.7, 151.5, 170.9 (2C); IR ($CHCl_3$) 3437, 2985, 1729, 1594, 1248 cm^{-1}; EI-MS *m/z* (% relative intensity) 456 (M^+, 71), 455 (100), 381 (44), 309 (46), 83 (12); HR-MS cacld for $C_{26}H_{24}N_4O_4$ 456.1798, found 456.1779.

6-(6-Phenyl-2-acetyl-2-(carboxyethyl)indan-5-yl)-9*H*-purine (3ccb). The deprotection of **3cbb** (80 mg, 0.16 mmol) afforded 45 mg (67%) of the title compound as a white solid: mp 109−110 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.22 (t, J = 7.2 Hz, 3H), 2.26 (s, 3H), 3.50−3.68 (m, 4H), 4.21 (q, J = 7.2 Hz, 2H), 6.99−7.03 (m, 2H), 7.07−712 (m, 3H), 7.39 (s, 1H), 7.52 (s, 1H), 8.39 (s, 1H), 8.76 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.8, 26.1, 38.0, 38.3, 61.6, 66.3, 126.1, 126.5, 126.5, 127.7 (2C), 128.70 (2C), 133.5, 139.0, 140.1, 140.6, 141.8, 151.5, 171.7, 202.5; IR (KBr) ν 2987, 2819, 1740, 1715, 1584, 1323, 1233 cm^{-1}; EI-MS *m/z* (% relative intensity) 426 (M^+, 32), 383 (25), 353 (21), 309 (18), 149 (40), 83 (47), 57 (100); HR-MS cacld for $C_{25}H_{22}N_4O_3$ 426.1692, found 426.1673.

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Supporting Information Available: Procedures for preparation of the starting material and spectral data of the benzyl protected arylpurines **3*xay*** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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