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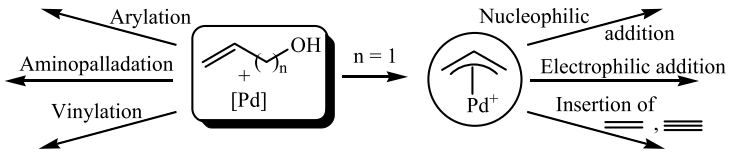
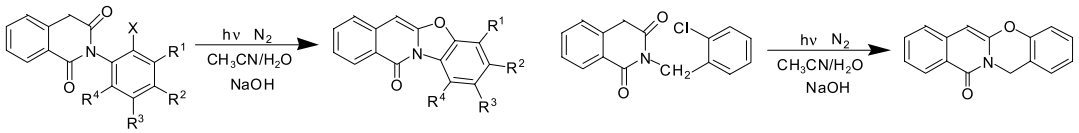
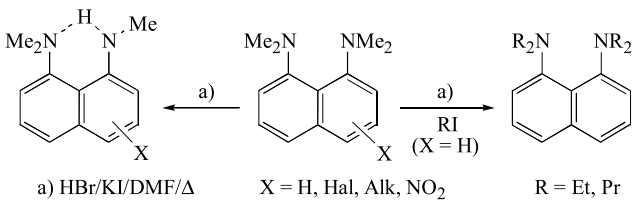
Contents

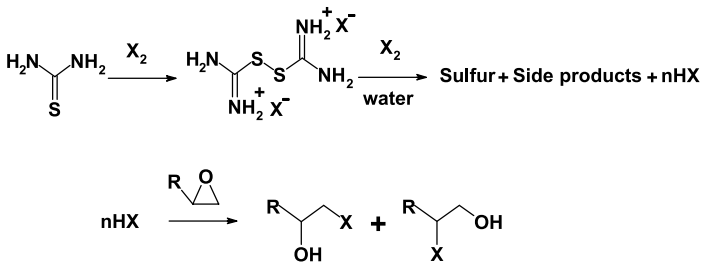
REPORT

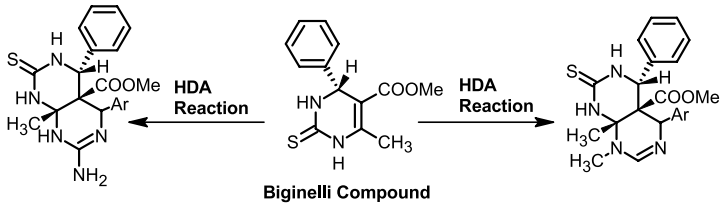


ARTICLES

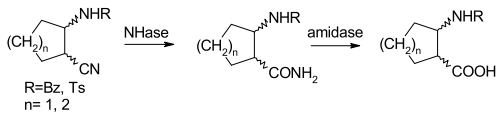


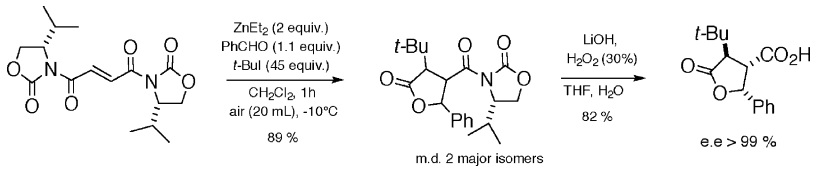


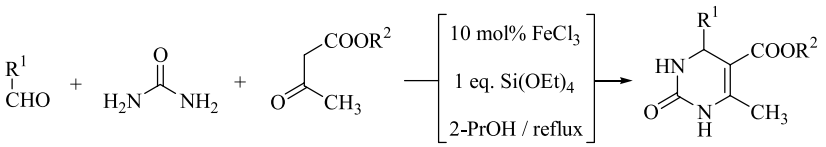




A number of potent pyrimido[4,5-*d*]pyrimidine analogues have been efficiently synthesized by hetero Diels–Alder cycloaddition. The molecular mechanism of the observed cycloaddition reaction has been investigated by means of theoretical studies at semiempirical PM3 level.

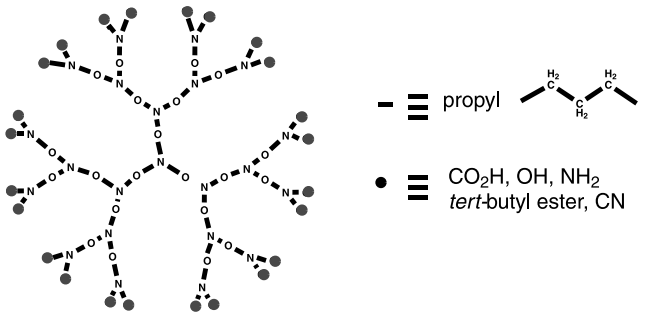


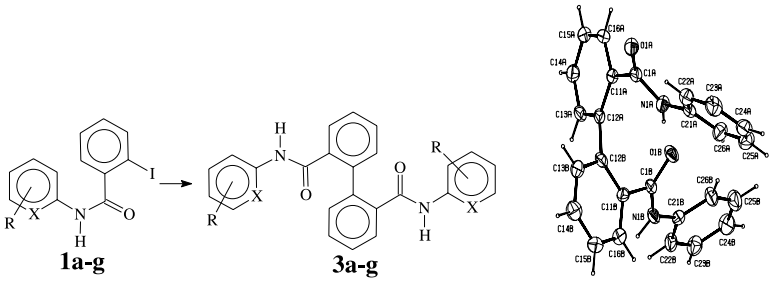


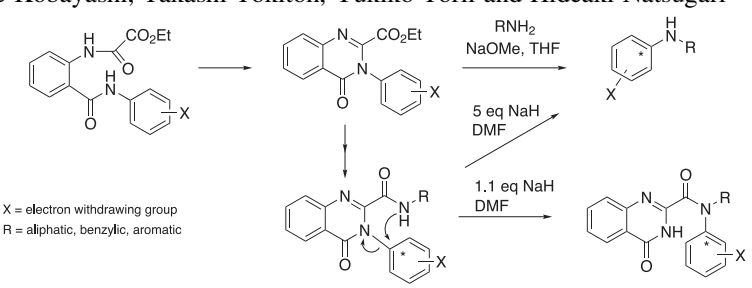


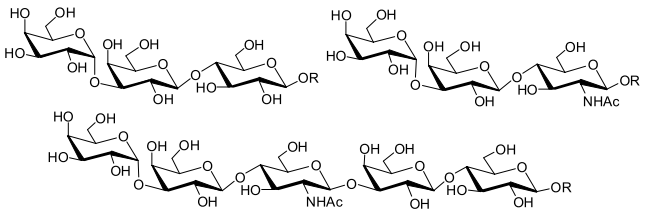
R^1 = various alkyls and aryls; R^2 = alkyls

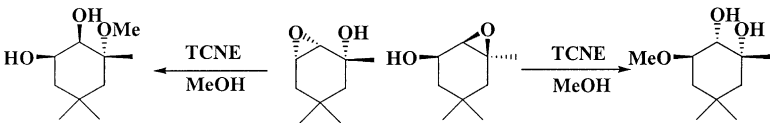
13 examples; Yields: 71-94%











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Palladium-catalysed reactions of alcohols. Part B: Formation of C–C and C–N bonds from unsaturated alcohols

Jacques Muzart*

Unité Mixte de Recherche 'Réactions Sélectives et Applications', CNRS, Université de Reims Champagne-Ardenne, B.P. 1039, 51687 Reims Cedex 2, France

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Contents

1. Introduction

The chemistry of alcohols occupies a central place in organic synthesis. Recently, we reviewed the palladium-catalysed oxidations of primary and secondary alcohols into their corresponding carbonyl compounds.[1] In fact, alcohols, either as substrates or reagents, lead to a variety of other useful reactions in the presence of catalytic amounts of palladium. Therefore, we will now attempt to provide, without exhaustive reference to literature reports, an overview of the panel of these other reactions with a series of reviews. In considering that the previous review is Part A,[1] the present report is Part B and this will be followed by Parts C and D which will mainly summarise the formation of C–O bonds, and the rearrangement, carbonylation and carboxylation reactions. Of course, some aspects are already documented in books and reviews, but the whole topic has never been specifically reviewed. Various reports describe the influence of the hydroxy group in multifunctionalized compounds on the reactivity or the selectivity of these compounds, even though the hydroxy group is recovered unmodified at the end of the process;[2] these reports and those concerning phenols are beyond the scope of the present reviews. In contrast, the reactions where the hydroxy group is not the driving force of the initial stage of the process, but is modified in the course of the subsequent palladium steps, will be highlighted. Some reactions at the borderline of the topic will also be included.

The reviews are organised firstly according to the type of reaction and secondly according to the nature of the substrate.

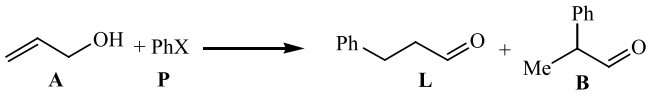
Keywords: Palladium; Alcohols; Arylation; Vinylation; Amination; η^3-Allylpalladium; Umpolung.

Abbreviations: BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; bmim, 1-*n*-butyl-3-methylimidazolium; Cy, cyclohexyl; cat., catalytic; conv., conversion; dba, dibenzylidene acetone; de, diastereoisomeric excess; DME, 1,2-dimethoxyethane; DMI, 1,3-dimethyl-2-imidazolidinone; ee, enantiomeric excess; equiv, equivalent; EWG, electron-withdrawing group; L, ligand; MS, molecular sieves; TON, turnover number; rt, room temperature; TPPTS, tris(3-sulfanatophenylphosphine) trisodium; Ts, *p*-toluenesulfonyl.

* Tel.: +33 3 2691 3237; fax: +33 3 2691 3166;
e-mail: jacques.muzart@univ-reims.fr

doi:10.1016/j.tet.2005.02.026

Table 1. Phenylation of allyl alcohol under different experimental conditions[a]



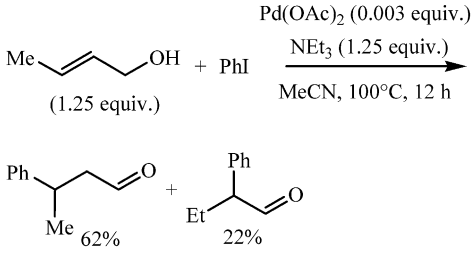
Entry	X	A:P	Catalyst (equiv)	Base (equiv) Additive (equiv)	Solvent	*t* (°C)	Time (h)	Yield (%) L, B
1[4]	I	1.25:1	$Pd(OAc)_2$ (0.003)	NEt_3 (1.25)	MeCN	100	0.5	60, 11
2[5]	I	1.5:1	$PdCl_2$ (0.009)	$NaHCO_3$ (1.2)	NMP	130	2	23, 10
3[17]	I	1.5:1	$Pd(OAc)_2$ (0.01–0.02)	$NaHCO_3$ (2.5) *n*-Bu_4NCl (0.95)	DMF	30	24	91, ?
4[30]	I	1.2:1	$Pd(OAc)_2$ (0.05), P(*o*-tol)$_3$ (0.1)	K_2CO_3 (2.4) *n*-Bu_4NCl (1)	MeCN/H_2O	MW	0.17	73, 16
5[36]	I	3:1	$Pd(OAc)_2$ (0.02), P(*o*-tol)$_3$ (0.1)	$NaHCO_3$ (2.5) *n*-Bu_4NCl (0.1)	H_2O	80	20	85, ?
6[14]	I	1:1	$PdCl_2$ (0.1)	$NaHCO_3$ (1.2)	*n*-Bu_4NBr	120	24	62, ?
7[61]	I	?	$Pd(OAc)_2$ (cat.)	$NaHCO_3$ (?)	DMF	Δ	1	90, ?
8[61]	OTf	?	$Pd(PPh_3)_4$ (cat.)	K_2CO_3 (?)	DMF	Δ	6	91, ?
9[61]	OTf	?	$Pd(PPh_3)_4$ (cat.)	NEt_3 (?)	DMF	Δ	6	87, ?
10[64]	N_2Cl	2:1	$PdCl_2$ (0.02) HCO_2Na (0.3)	AcONa (3)	MeCN/H_2O	rt	1.5–2	37,4
11[65]	N_2BF_4	1.5:1	$Pd(OAc)_2$ (0.02)		EtOH	60	4	41, ?

[a] ?, not mentioned; Δ, heating; MW, microwave irradiation (140 W).

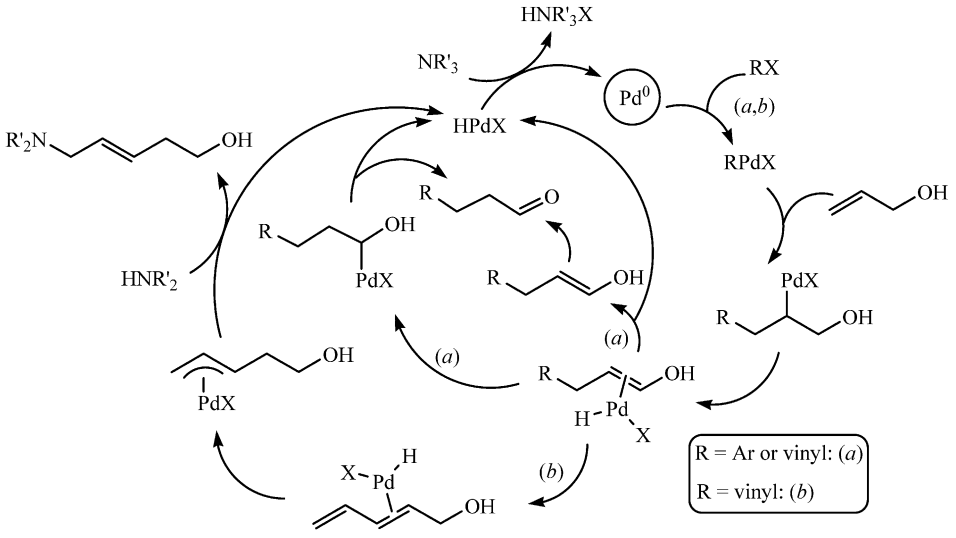
2. Arylation and vinylation

2.1. Intermolecular reactions

In 1968, Heck disclosed the formation of 3-aryl aldehydes and ketones by the reaction of primary and secondary allylic alcohols with arylpalladium complexes prepared in situ from arylmercuric chlorides or acetates and either an equimolecular amount of a palladium^{II} salt, or a catalytic amount of this salt with an equimolecular amount of copper^{II} chloride to regenerate the palladium after each reaction cycle.[3] In 1976, the teams of Heck and Chalk reported simultaneously, but independently, a strong improvement in these couplings by disclosing that such compounds are also obtained using aryl iodides or bromides instead of arylmercuric salts and, furthermore, with a catalytic amount of a palladium catalyst (Table 1, entries 1 and 2; Eq. 1)[4,5] via a reaction involving Pd^0 catalysis, even though $Pd(OAc)_2$ is often used as the starting catalyst, the Pd^{II} salt being reduced in situ to form the catalytically active Pd^0 complex.[6] A conventional, but probably oversimplified,[7] catalytic cycle for the formation of the adducts is illustrated in Scheme 1, path *a* (R=Ar).[8,9] For these reactions, the favourable abstraction of a β-hydrogen adjacent to oxygen in preference to a benzylic hydrogen may be highlighted.

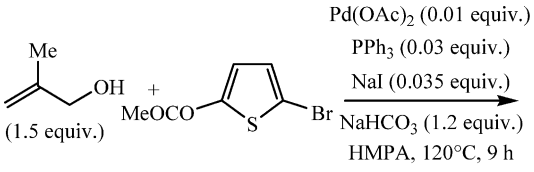


(1)



Scheme 1.

After Heck's and Chalk's reports, the coupling was quickly extended to thienyl bromides (Eq. 2)[10] and the synthesis of β-substituted aldehydes or ketones from (hetero)arylation of α,β-allylic alcohols is now considerably documented, nabumethone, a non-steroidal anti-inflammatory drug, being an example (Eq. 3).[11–16]



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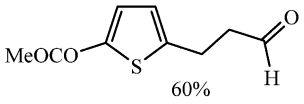
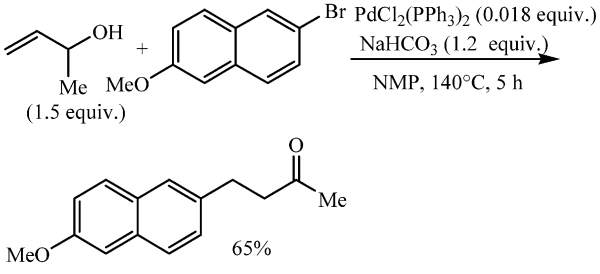
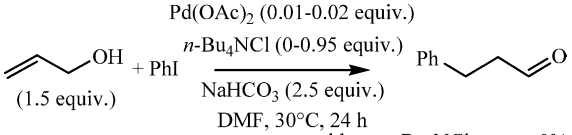




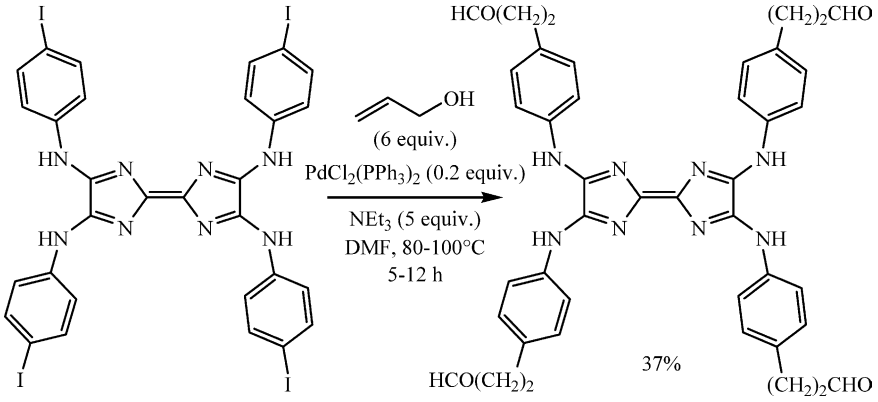
(3)

In 1984, Jeffery has shown that stoichiometric quantities of ammonium salts facilitate the Heck arylation of allylic alcohols (Table 1, entry 3; Eq. 4).[17] Although subsequent arylations of allylic alcohols have been sometimes carried out in the absence of ammonium halides (Eqs. 5 and 6),[18–22] they have been mostly performed using stoichiometric amounts of ammonium halides in organic solvents (Table 1, entry 4; Eq. 7)[23–35] or catalytic amounts of n-Bu_4NCl in water (Table 1, entry 5; Eq. 8).[36] Interestingly, Jeffery's conditions allow the selective transformation of the iodine atom of 1-bromo-2-iodobenzene (Eq. 9).[32–35]



(4)

without n-Bu_4NCl, conv.: 0%
with n-Bu_4NCl (0.4 equiv.), conv.: 61%, yield: 47%
with n-Bu_4NCl (0.95 equiv.), conv.: 100%, yield: 91%



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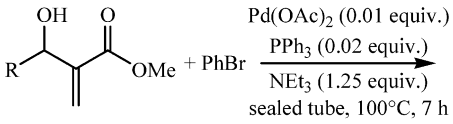
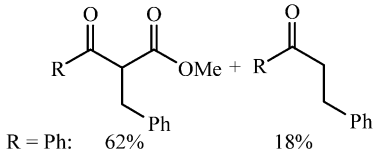
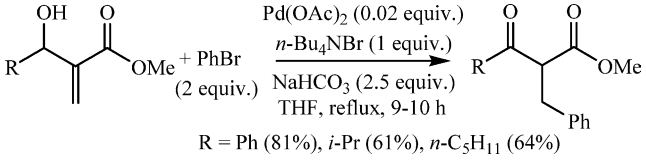


(6)





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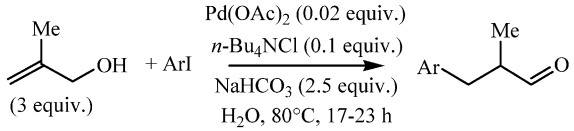
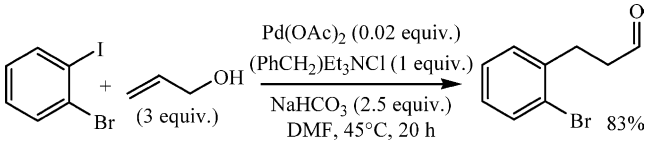


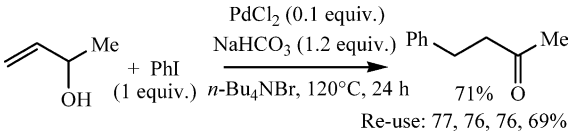
Ar = Ph (81%), p-ClC_6H_4 (83%), p-$MeOC_6H_4$ (80%), p-MeC_6H_4 (75%)

(8)

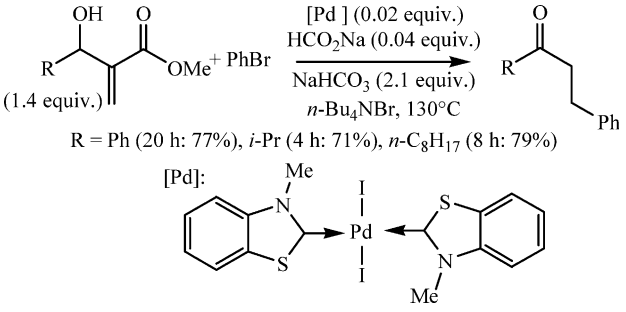


(9)

The Jeffery procedure for the Heck arylation urged us to investigate the reaction in molten tetra-n-butyl ammonium bromide as solvent and these new conditions allowed us to recycle both the catalyst and the ammonium salt (Table 1, entry 6; Eq. 10).[14] Instead of $PdCl_2$ as catalyst, Caló et al. have used the 1:2 association of a Pd-benzothiazole carbene complex and sodium formate to perform the same transformations.[15,16] The arylation of the Baylis–Hillman adducts under Caló's conditions is accompanied by complete decarbomethoxylation (Eq. 11);[16,37] this contrast with the results of Bhat et al.[19] and Basavaiah et al.,[28] who have carried out the coupling in the absence of solvent or in refluxing THF, respectively (Eqs. 6 and 7).

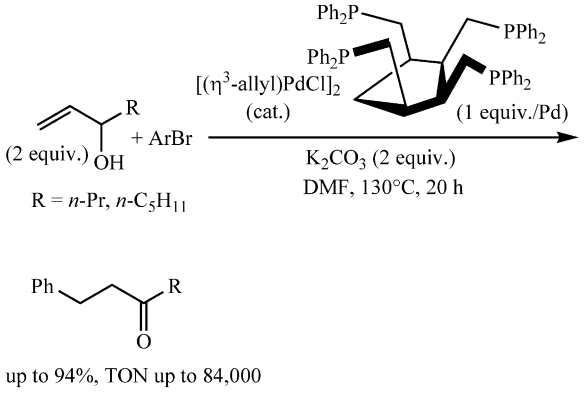


(10)



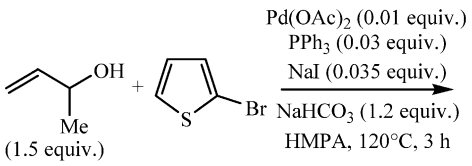
(11)

Recently, the arylation of alk-1-en-3-ols with a range of aryl bromides has led to the corresponding ketones with high turnover numbers using $[(\eta^3\text{-allyl})PdCl]_2$ associated with the Doucet/Santelli ligand as the catalytic system (Eq. 12).[38]



(12)

In some cases, a mixture of α- and β-substituted carbonyl compounds is obtained, the latter being nevertheless predominant (Table 1, entries 1, 2 and 4; Eqs. 1, 13 and 14)[10,14,15,26,30,39–41] and may become the unique isomer in optimising the reaction conditions (Eq. 14).[26] A side product can be the β-substituted α,β-unsaturated carbonyl compound,[41] especially when the reaction is carried either under an air atmosphere[40] or in the presence of $Cu(OTf)_2$ (Eq. 15).[42] In fact, it has been shown that a portion of the initial substrate was oxidised under these conditions,[40–42] and it is surprising that such adducts are not more usually obtained, since the Pd^{II}-catalysed oxidation of alcohols with aromatic bromides as re-oxidants of palladium species is an efficient process.[1,43]



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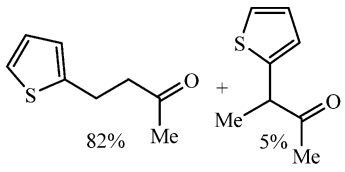

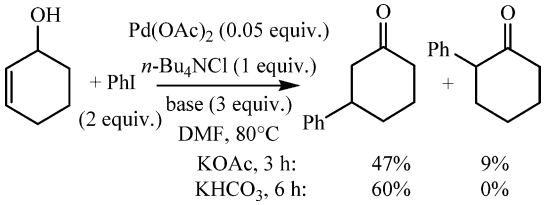

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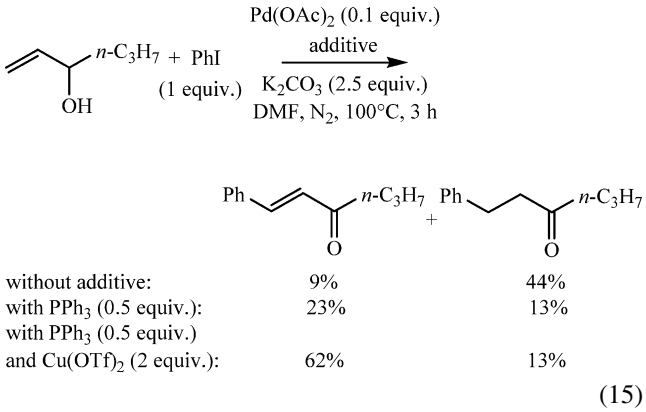
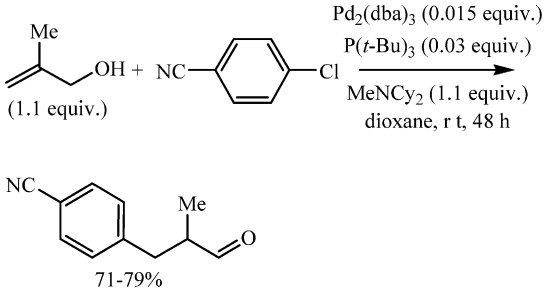


(15)

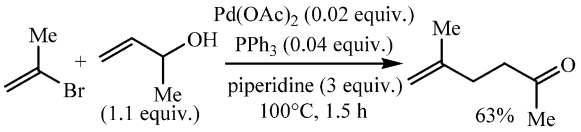
Activated aryl chlorides are also effective arylating agents, even at room temperature, when the $Pd_2(dba)_3/P(t\text{-}Bu)_3/MeNCy_2$ system is employed (Eq. 16).[44]

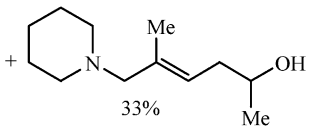


(16)

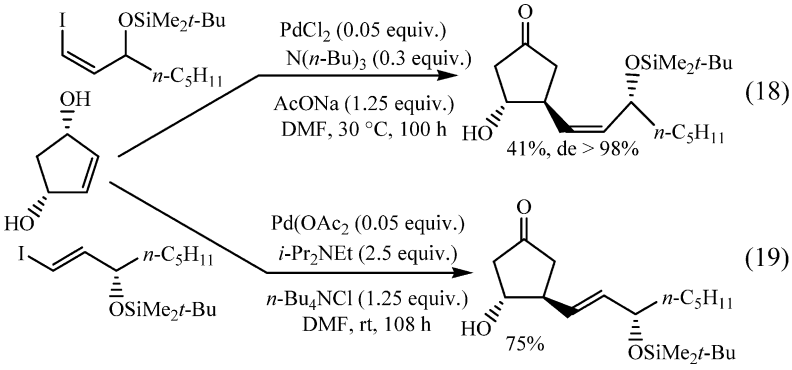
In extending the coupling process to the vinylation of allylic alcohols, Heck et al. have observed that piperidine or morpholine instead of triethylamine is often required as the acid acceptor to obtain a significant coupling and this leads generally to a mixture of the 3-vinyl aldehyde or ketone and to the aminoalkenol (Eq. 17; Scheme 1, path *b*).[45,46] Nevertheless, modifications of the experimental conditions have allowed the synthesis of prostaglandin analogues by coupling of vinylic iodides with *meso*−2-cyclopentene-1,4-diol (Eqs. 18 and 19)[47,48] or its optically active mono-protected form[49] in the absence of secondary amines. Torii et al. have observed that the alkenylation of 2-cyclopentenol

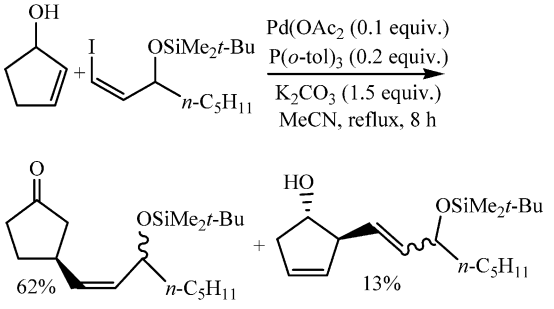
occurs at both olefinic carbons, the minor reactive site being the C2 center (Eq. 20).[47]





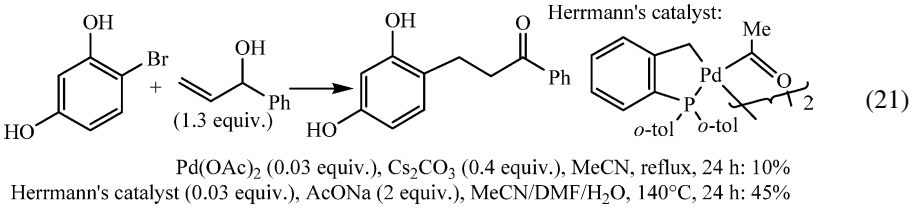
(17)





(20)

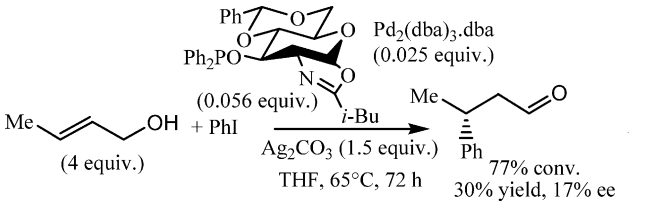
A variety of dihydrochalcones have been synthesized via the coupling of aryl halides and 1-aryl-2-propen-1-ols, the yield in some cases being highly dependent on the experimental conditions (Eq. 21).[50]



(21)

Pd(OAc)$_2$ (0.03 equiv.), Cs_2CO_3 (0.4 equiv.), MeCN, reflux, 24 h: 10%
Herrmann's catalyst (0.03 equiv.), AcONa (2 equiv.), MeCN/DMF/H_2O, 140°C, 24 h: 45%

Uemura et al. have reported the first enantioselective phenylation of allylic alcohols using *trans*- and *cis*-crotyl alcohols as substrates; this reaction, which introduces the chirality on the β-carbon, provided the corresponding β-phenylated aldehyde with a low ee (Eq. 22).[51] Exploratory studies to obtain the chirality in the α-position by phenylation of 2-substituted allylic alcohols have been disappointing.[52,53]

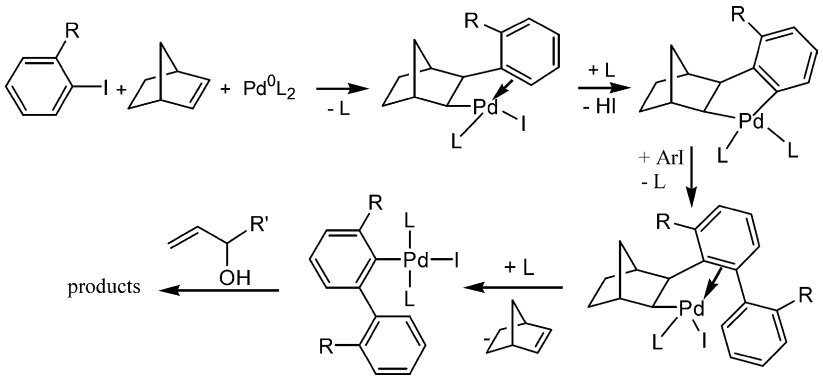


(22)

In contrast to 1-bromo-2-iodobenzene, 1,2-diiodobenzene may show a sluggish performance with unsaturated alcohols.[34,35,54] Nevertheless, diiodobenzenes and in particular, 1,2-diiodobenzene, have been used with either bisallylic alcohols to synthesize oxo-functionalized macrocycles (Eq. 23),[55] or allyl alcohol to obtain benzocyclohept-2-ene-2-carboxaldehyde, this latter compound resulting from the in situ intramolecular condensation of the intermediate biscarbaldehyde (Eq. 24).[54] As for 1,8-diiodonaphthalene, its coupling reaction with allylic and homoallylic alcohols can lead to the annulation products via the carbopalladation of the olefinic component followed by an Ullmann-type ring closure (Eq. 25), or to carbonyl compounds.[54]

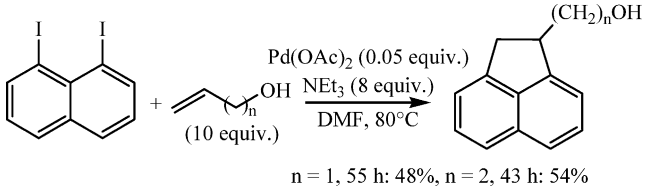
In collaboration with Catellani's team, we have disclosed the synthesis of substituted biphenyls containing an oxoalkyl chain through a domino reaction starting from iodoarenes and allylic alcohols under the catalytic action of palladium and norbornene (Eq. 26).[56] This process was based on Catellani's key reaction, which implies the temporary insertion of norbornene into a palladacycle (Scheme 2).[57]

Instead of vinyl and aryl halides, Tsuji et al. have added $BrCCl_3$ and CCl_4 to various secondary allylic alcohols and obtained γ-trichloro ketones.[58,59] The use of primary allylic alcohols led to a mixture of carbonyl compounds, due to the Pd-catalysed oxidation of the alcohol prior to the reaction



Scheme 2.

with $XCCl_3$. In fact, the mechanism of the formation of these γ-trichloro ketones differs from that summarised in Scheme 1. This is exemplified by the reaction of 1-hepten-3-ol, which affords either 1,1,1-trichloro-4-octanone or the halohydrin, depending on the reaction temperature (Scheme 3, paths *a* and *b*). This observation has led to a new procedure for the conversion of various halohydrins to ketones (Scheme 3, path *c*).[59,60]



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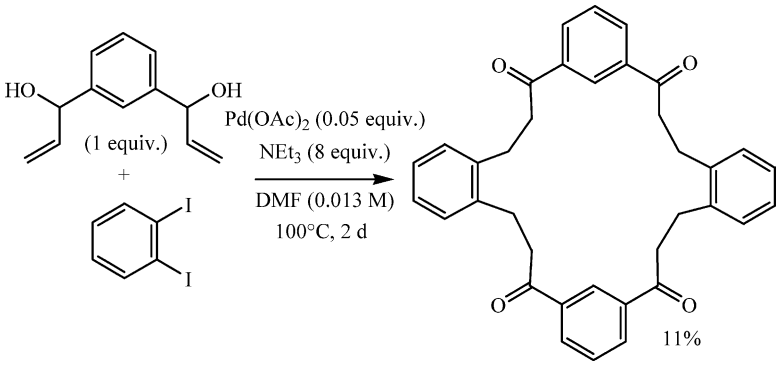

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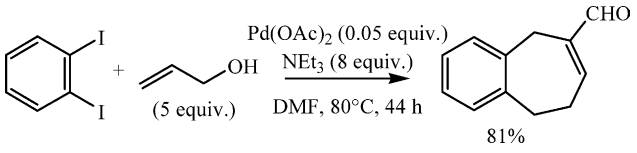
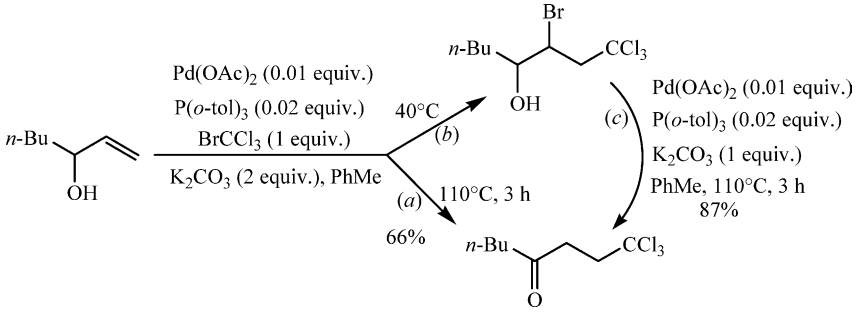


(24)

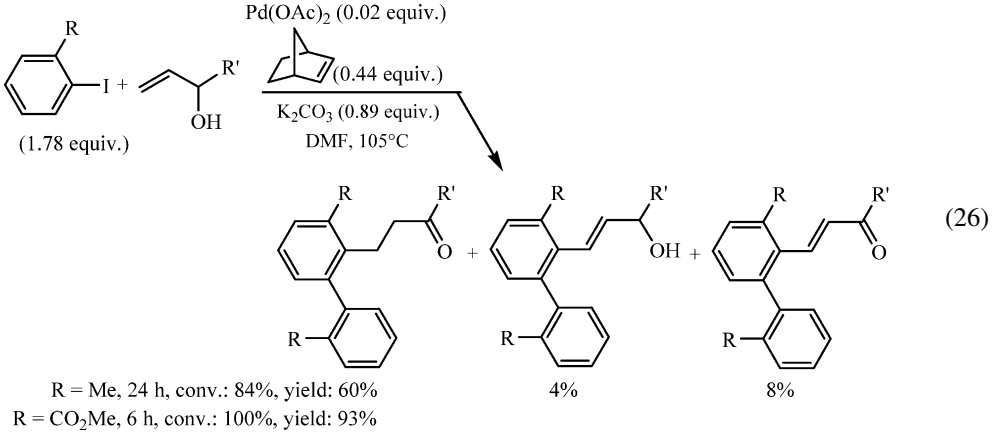
Kang et al. have briefly mentioned the use of phenyl triflate for the effective arylation of allyl alcohol (Table 1, entries 8 and 9),[61] while Nishimura et al. reported the use of diaryliodonium bromides for the $Pd_2(dba)_3$-catalysed synthesis of β-substituted aldehydes from allyl alcohol and 2-methyl-2-propenol in a basic organic medium.[62]

Matsuda et al. have carried out the arylation of primary allylic alcohols using arenediazonium chlorides in aqueous



Scheme 3.

acetonitrile in the presence of sodium acetate (Table 1, entry 10),[63,64] while the Cai team has used arenediazonium tetrafluoroborates in ethanol, under base-free conditions, to obtain β-arylated carbonyl compounds from various primary and secondary alcohols (Table 1, entry 11; Eq. 27).[65]



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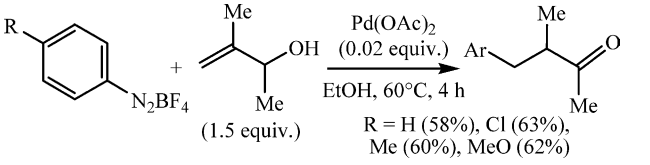
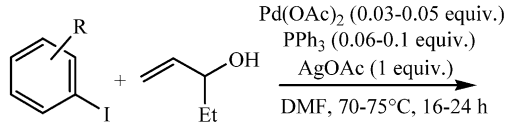


(27)

Jeffery has disclosed that the substitution of primary and secondary allylic alcohols by aryl iodides[24] or 1-alkenyl iodides[66,67] can proceed without 'isomerisation' of the double bond provided that a stoichiometric amount of a silver salt, AgOAc or Ag_2CO_3, was used as an additive (Eqs. 28 and 29), and this procedure has been retained by Tietze et al. for approaches to the synthesis of vitamin E (Eqs. 30 and 31).[31] Another method proposed by Kang et al. for arylations and alkenylations without 'isomerisation' of the double bond is the use of hypervalent iodonium tetrafluoroborates (Eq. 32).[61,68]



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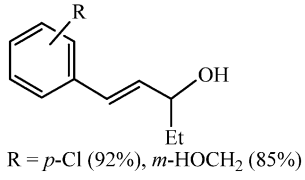

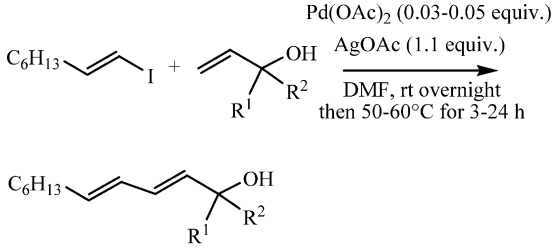

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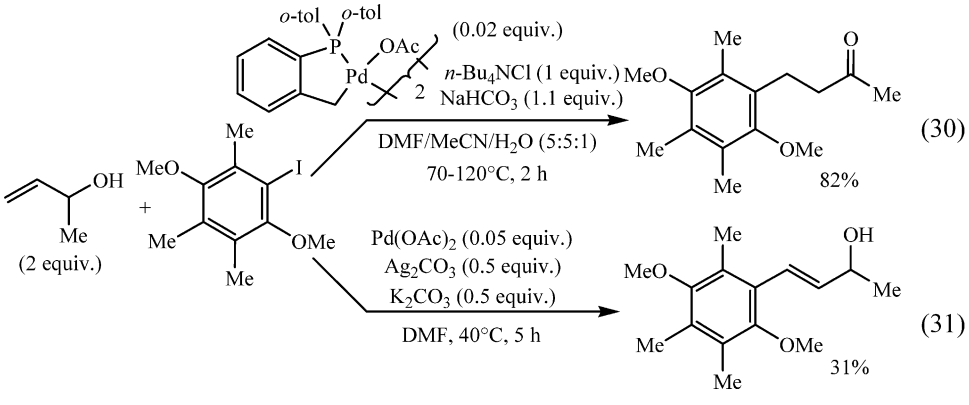
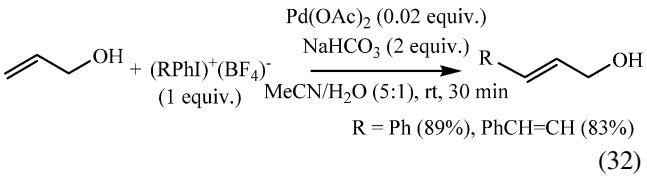


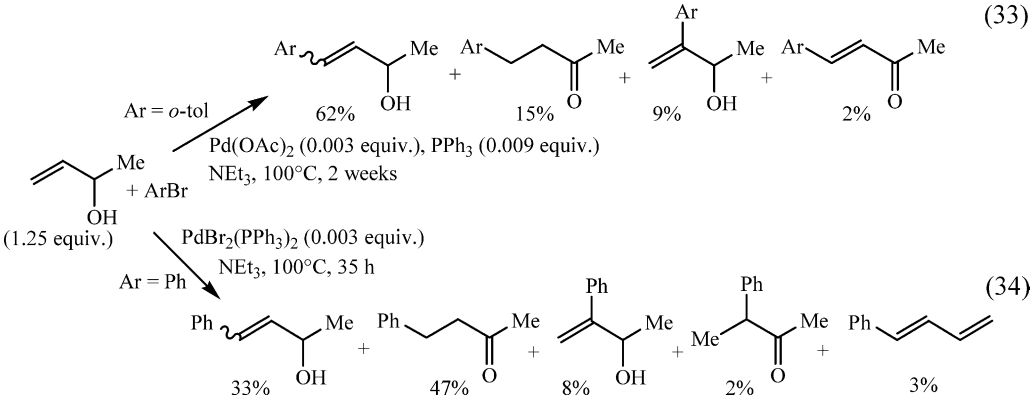
(30)

(31)



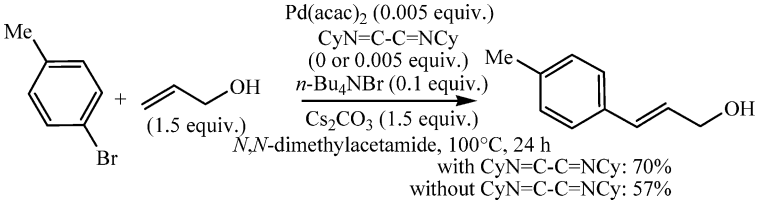
(32)

The above selective syntheses of β-substituted allylic alcohols assisted by silver salts have been disclosed for alcohols having a terminal double bond; these could be restricted to such substrates, since the Pd-catalysed phenylation of *trans*- and *cis*-crotyl alcohols in the presence of Ag_2CO_3 led to aldehydes (Eq. 22).[51] Some β-substituted allylic alcohol is sometimes obtained in the absence of a silver salt, but rather from secondary (Eqs. 33 and 34)[4,69] than primary allylic alcohols.[4,44,46] Nevertheless, 3-tolyl-2-propen-1-ol has been selectively produced from allyl alcohol, 4-bromotoluene, $Pd(acac)_2$, *n*-Bu_4NBr and Cs_2CO_3 in *N*,*N*-dimethylacetamide (Eq. 35);[70] this contrasts with the usual reactivity of this alcohol summarised in Table 1.



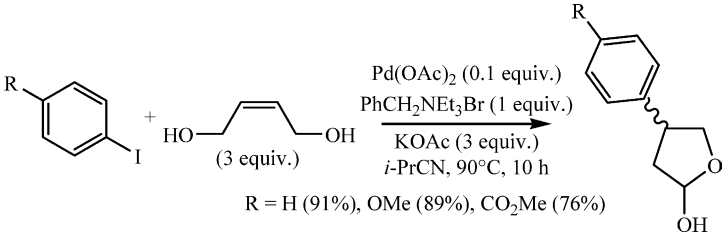
(33)

(34)



(35)

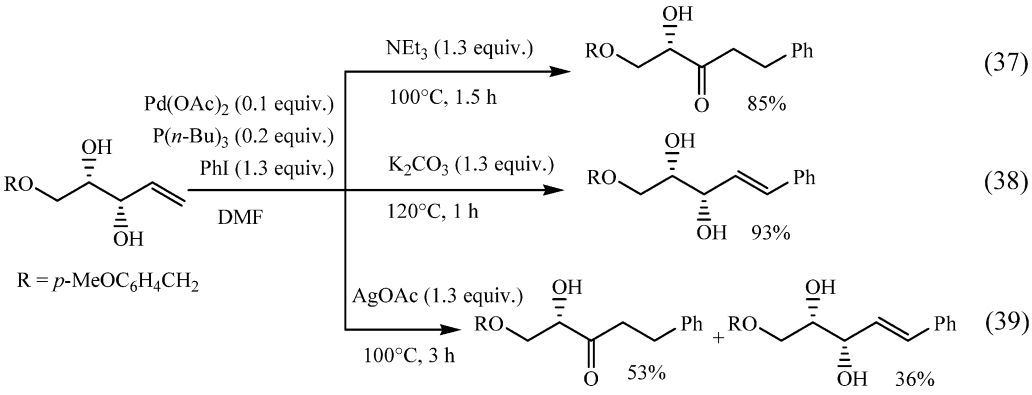
With (*Z*)-2-butene-1,4-diol as substrate, Mandai et al. have synthesized a variety of 4-substituted 2-hydroxytetrahydrofurans by reaction with aryl iodides (Eq. 36) or 1-alkenyl halides.[71] In fact, the phenylation of this substrate was previously carried out by Chalk et al., but the adduct dehydrated upon distillation to give 3-phenyl-2,3-dihydrofuran.[5]



(36)

Kang et al. have reported a dramatic influence of the nature of the base on the regioselection of the β-H elimination with allylic α-diols as substrates and phenyl iodide as arylating agent, obtaining the α-hydroxyketone with NEt_3, the α-diol with M_2CO_3 (M_2 = Na_2, NaH, K_2, Cs_2) and a mixture of both compounds with AgOAc (Eqs. 37–39).[72] With K_2CO_3 as base, Cheeseman et al. obtained optically active 4-aryl-3-butene-1,2-diols from the arylation of (2*R*)-3-butene-1,2-diol with aryl bromides, but, curiously, with some loss of the enantiopurity, the degree of this deterioration being marked with an electron-rich aryl bromide (Eq. 40).[73] It should also be noted that the yields obtained by Cheeseman et al. for these arylations were modest and that Nokami et al. reported the lack of reactivity of bromobenzaldehyde with a 3,4-dihydroxy-1-alkene.[74]

According to Kang et al., the dependence of the regioselection depicted in Eqs. 37–39 is not observed in the absence of the diol functionality.[72] Nevertheless, the nature of the base seems to have an important role on the selectivity of the arylation of allylic alcohols in water; indeed, Cai et al. obtained selectively the β-aromatic carbonyl compounds with $NaHCO_3$ and catalytic amounts of both $Pd(OAc)_2$ and *n*-Bu_4NCl, while the use of Na_2CO_3 in place of $NaHCO_3$ increased strongly the quantity of the β-arylated α,β-unsaturated alcohols.[36]



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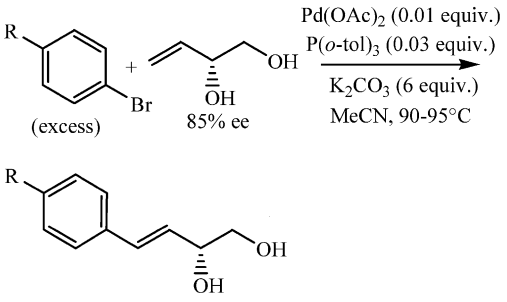
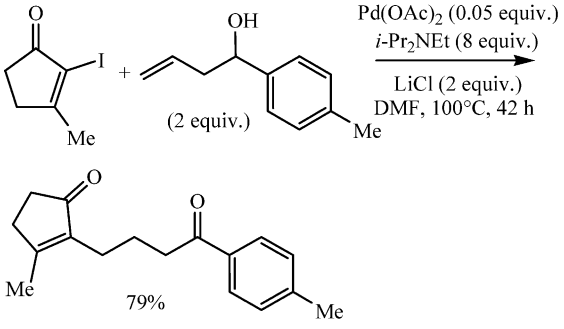


(40)

R = OMe (35% yield, 66% ee); Ac (29% yield, 80% ee)

The reaction of vinyl, aryl and heteroaryl halides with homoallylic alcohols can afford the corresponding β-substituted ketones (Eq. 41)[10,75–77] or aldehydes (Eq. 42).[34,35] Fair to high yields of substituted aldehydes have been obtained, even from either 10-undecen-1-ol and phenyl iodide (Eq. 43)[23] or 2-methyl-11-dodecen-1-ol and 3-iodopyridine (Eq. 44),[78] although the arylation of homoallylic alcohols can occur without the migration of the double bond (Eq. 45).[54,72]



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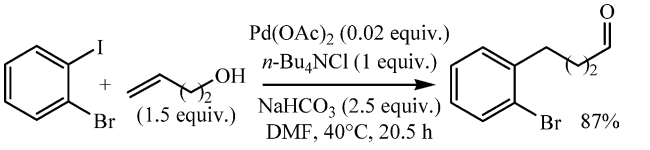

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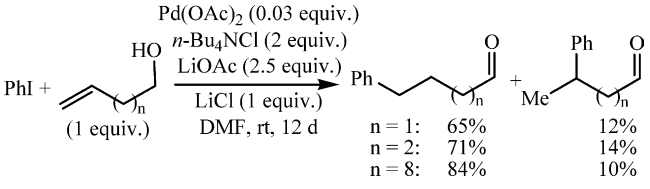
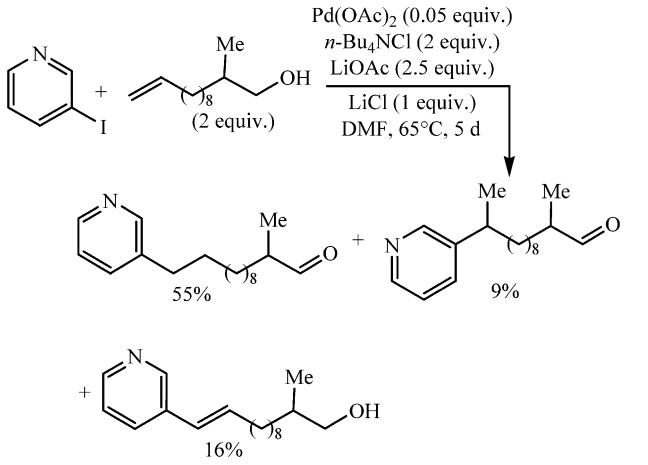
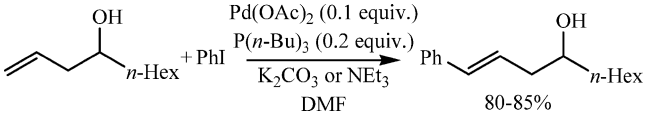


(43)

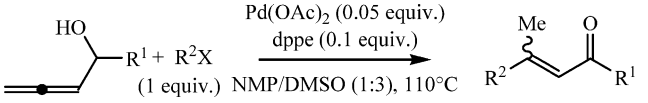


(44)



(45)

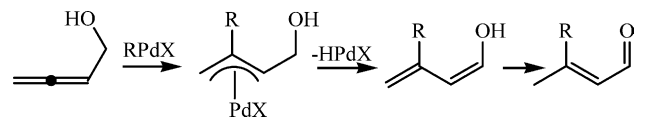
Tsuji et al. have obtained β-aryl- and β-alkenyl-β-methyl-α,β-unsaturated carbonyl compounds from primary or secondary 1,2-dien-4-ols and aryl or alkenyl halides (Eq. 46).[79,80] The products arise from the dehydrogenation of the η^3-allylpalladium intermediates[81] (Scheme 4), this step probably being facilitated by the tertiary amine,[82] which was used in excess.



R^1 = H, R^2X = PhI, 0.8 h: 88%; R^1 = H, R^2X = PhCH=CHBr, 4 h: 69%
R^1 = Ph, R^2X = PhI, 1.5 h: 65%; R^1 = Ph, R^2X = PhCH=CHBr, 1.5 h: 94%
R^1 = *i*-Bu, R^2X = PhCH=CHBr, 4 h: 77%
R^1 = *i*-Bu, R^2X = *p*-HCOC$_6$H$_4$Br, 3 h: 61%

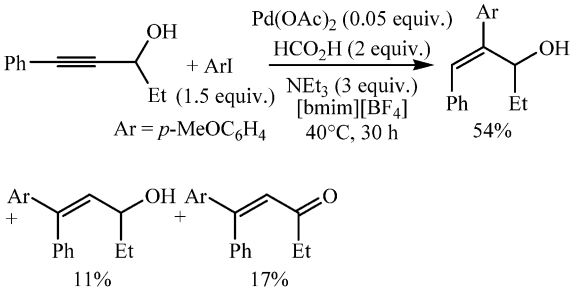
(46)

The addition of arylpalladium complexes to disubstituted alkynes leads to 2-aryl-vinylpalladium intermediates, the



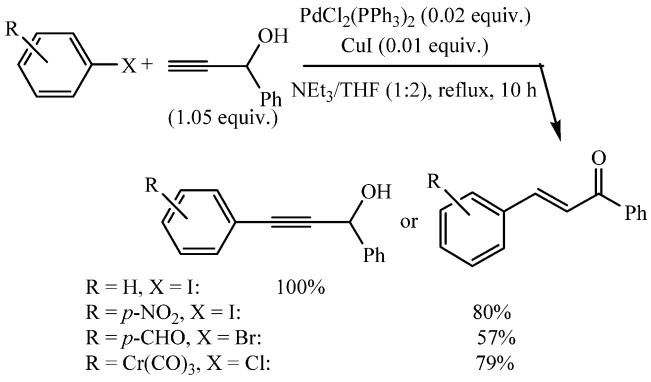
Scheme 4.

reduction of which by hydrides affords the trisubstituted alkenes;[83] the application of this hydroarylation process to secondary propargylic alcohols in DMF[84] or ionic liquids[85] affords β-arylated α,β-unsaturated ketones as side products (Eq. 47). According to Cacchi et al., the carbopalladation adduct, which leads to the β-arylated α,β-unsaturated alcohol, also gives the arylated allenyl alcohol via competitive β-elimination of HPdI species, and the isomerisation of this allenyl alcohol affords the corresponding unsaturated ketone.[85]



(47)

Although the Sonogashira reaction of aryl halides with primary and secondary propargylic alcohols usually leads to the corresponding coupling products without affecting the hydroxy group, β-substituted-α,β-unsaturated ketones have been obtained from 1-aryl(or heteroaryl)-2-propyn-1-ols when the halide partner bears an electron-withdrawing group (Eq. 48),[86] or is a 6-iodouracil (Eq. 49),[87,88] a 5-halo-3(2*H*)-pyridazinone (Eq. 50),[89,90] or a heteroaromatic iodide containing a nitrogen attached to the carbon bearing the iodine atom (Eq. 51).[91] According to the authors, these reactions involve the substituted propargylic alcohols as intermediates, and the formation of the corresponding ketones occurs from their base-mediated isomerisation,[86,89–91] rather than via palladium intermediates.[87a,88,92] The isomerisation is greatly dependent on the propargylic alcohol substituent,[89–91,93] the nature of the halide partner,[86,92,94] and/or the reaction temperature.[95] As examples, the isomerisation did not occur from the coupling of propargyl alcohol with *p*-nitrophenyl iodide[96] or bromide, even at 80 °C (Eq. 52),[94] while the isomerisation of 3-(2-pyridyl)-2-propyn-1-ol to 3-(2-pyridyl)acrylaldehyde in diethylamine at 80 °C would require a metal catalyst.[92] The particular coupling/isomerisation reaction of 1-aryl(or heteroaryl)-2-propyn-1-ols has been intensively exploited as the starting step of the synthesis of numerous heterocycles.[97]



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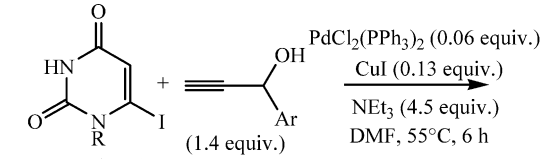
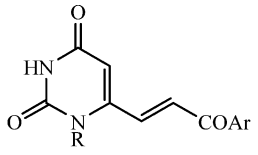
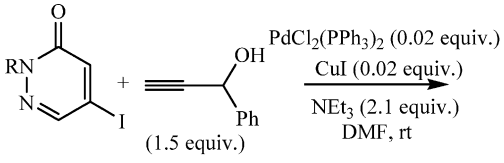
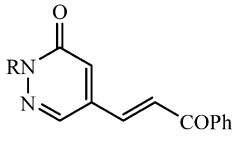




Ar = Ph (92%), *p*-MeC_6H_4 (71%), *p*-$MeOC_6H_4$ (91%), *o*-$MeOC_6H_4$ (70%)

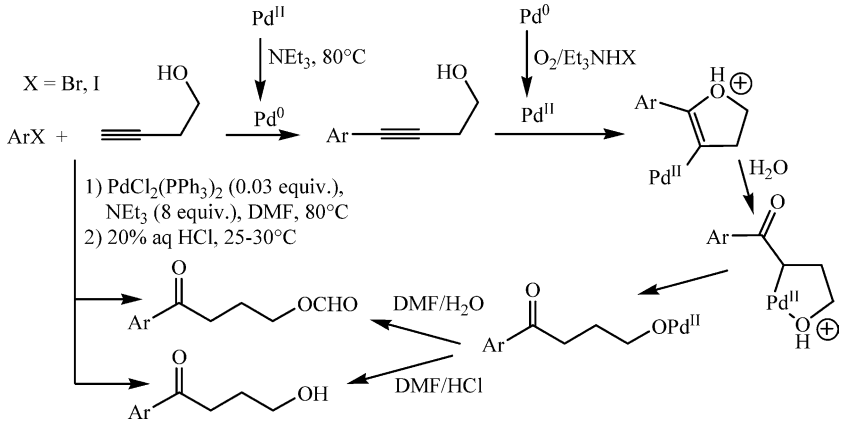
(49)



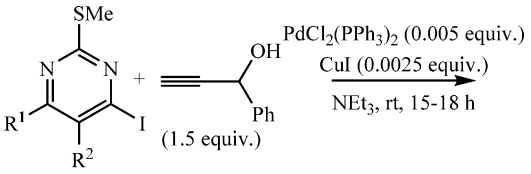


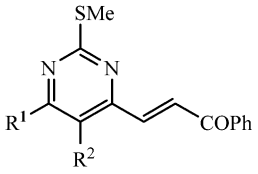
R = Me (89%), CH_2Ph (70%)

(50)



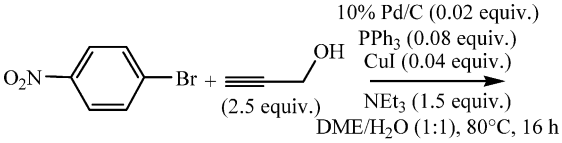
Scheme 5.



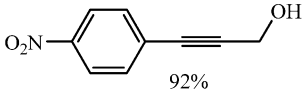


R^1 = Me, R^2 = H: 44%; R^1 = R^2 = Me: 21%; R^1 = H, R^2 = OMe: 62%
R^1 = R^2 = OMe: 73%; R^1-R^2 = CH_2SCH_2: 36%

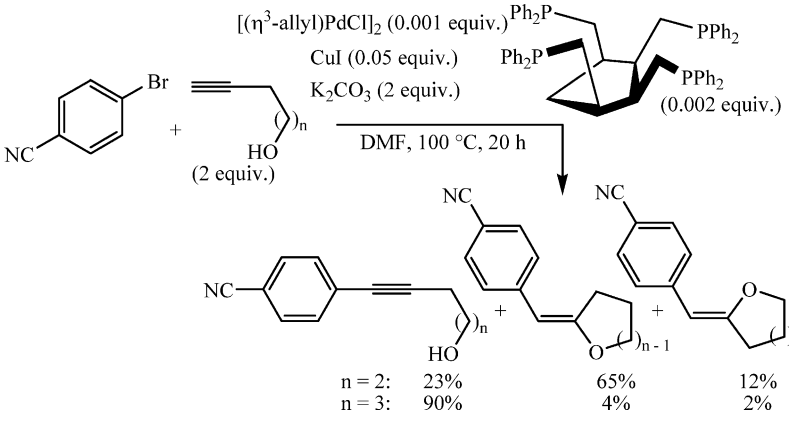
(51)



(52)



The Sonogashira reaction of aryl bromides with pent-1-yn-5-ol and hex-1-yn-6-ol evolves, in some cases, towards the cyclisation products (Eq. 53).[98]

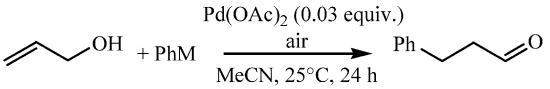


(53)

In the copper-free Sonogashira-hydration strategy using aryl halides and 3-butyn-1-ol, it has been suspected that the addition of the hydroxyl group to the triple bond has a key role in the regioselectivity of the hydration process (Scheme 5).[99]

Various carbon carbon coupling procedures using tertiary propargylic alcohols as substrates led to the concomitant cleavage of the C–CR_2OH bond which will be documented in Part D of this series of reviews.

As noted at the beginning of this section, arylmercuric salts were initially used for the Heck reaction of allylic alcohols, the regeneration of the active palladium species being assumed by $CuCl_2$.[3,100] In fact, this coupling was mainly developed using stoichiometric amounts of palladium^{II} salts for the synthesis of prostaglandin analogues[48] and *C*-glycosides.[101] Uemura et al. examined the efficiency of other organometallic salts, with $Pd(OAc)_2$ as catalyst, and an air atmosphere to regenerate the active Pd^{II} species: the phenylation of allyl alcohol proceeded well with Ph_2SbCl and Ph_2BiCl, while $PhSbCl_2$, Ph_2TiCl, Ph_3SnCl, Ar_2TeCl_2 were much less effective (Eq. 54).[102] According to these authors, the catalytic cycle does not imply decomposition of the HPdOAc intermediate into Pd^0, but rather participation of oxygen to regenerate PhPdOAc (Eq. 55).

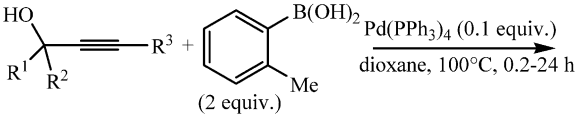


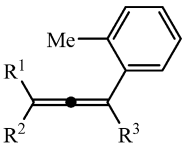
(54)

PhM = Ph_2SbCl (0.8 equiv.): 94%; Ph_2BiCl (1.2 equiv.): 61%
$PhSbCl_2$ (1 equiv.): 9%; Ph_3SnCl (0.8 equiv.): 3%

$$HPdOAc + Ph_2SbCl + O_2 \rightarrow PhPdOAc + PhSbO_2 + HCl \quad (55)$$

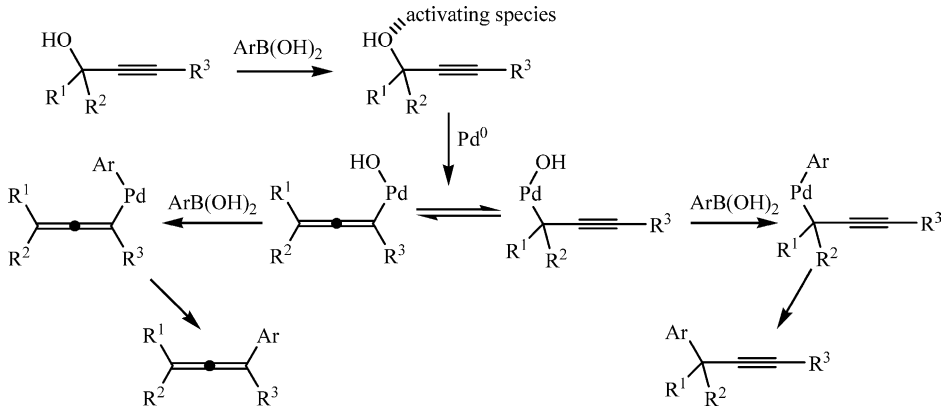
The coupling of arylboronic acids with secondary or tertiary propargylic alcohols afforded the corresponding allenic arenes (Eq. 56), while a mixture of allenic and propargylic arenes was mostly obtained with primary propargylic alcohols (Eq. 57). A mechanism involving the activation of the substrate by the boronic acid, or a proton derived from the boronic acid, is plausible (Scheme 6), but the low enantiomeric excess of the coupling product when using a chiral propargylic alcohol (Eq. 58) suggested the formation of other intermediates.[103]



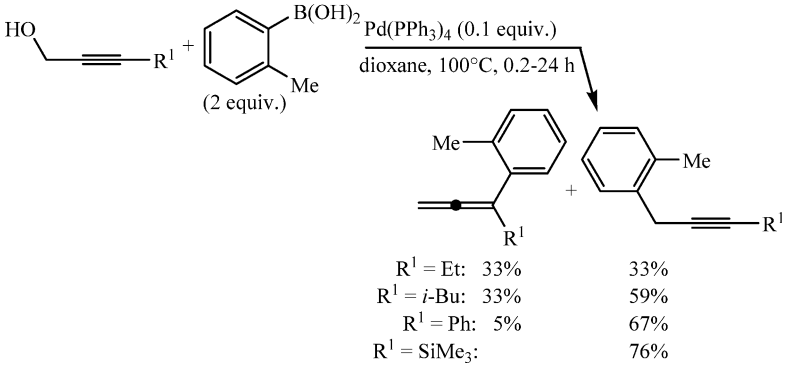


R^1 = Me, R^2 = Ph, R^3 = H: 99%; R^1 = R^2 = Ph, R^3 = H: 67%
R^1 = Ph, R^2 = R^3 = H: 89%; R^1 = Ph, R^2 = H, R^3 = $(CH_2)_3Me$: 79%

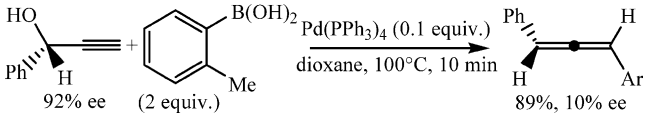
(56)



Scheme 6.



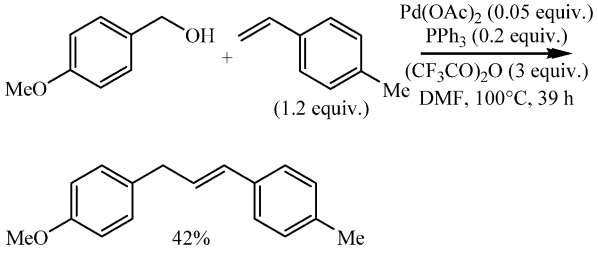
(57)



(58)

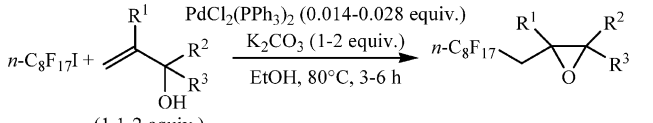
Before closing this section, it would be useful to include two studies which, in fact, describe neither an arylation or an vinylation reaction but, nevertheless, involve a Heck-type coupling.

Shimizu et al. have disclosed the benzylation of *p*-methylstyrene in the presence of trifluoracetic anhydride (Eq. 59). This process, studied after observing the Pd-catalysed benzylation of olefins with benzyl trifluoroacetates, would occur via the Heck-type addition of the benzyl(trifluoroacetato)palladium complex to the C=C bond.[104]



(59)

Fuchikami et al. have synthesized polyfluoroalkylmethyl-substituted oxiranes via the coupling of polyfluoroalkyl halides with allylic alcohols (Eq. 60). This domino reaction involves the formation of both C–C and C–O bonds and, according to the postulated mechanism (Scheme 7), the formation of the oxopalladacycle intermediate from **A** rather than that of the double bond via the β-H elimination, is due to interactions between the palladium center and fluorine atoms.[105]

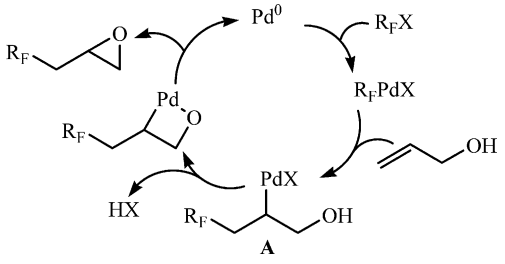


$R^1 = R^2 = R^3 = = H$: 70%; $R^1 = R^2 = H$, $R^3 = Me$: 69%
$R^1 = H$, $R^2 = R^3 = Me$: 79%; $R^1 = Me$, $R^2 = H$, $R^3 = Et$: 56%

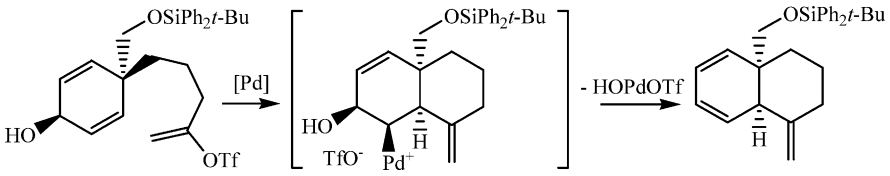
(60)

2.2. Intramolecular reactions

The first Pd-catalysed intramolecular reaction was reported by Heck et al. in 1983 using 2-bromoallyl 4-hydroxy-2-butenyl ether (Eq. 61).[106] In contrast, 5-bromo-5-hexenyl 4-hydroxy-2-butenyl ether led to very little, if any, cyclic product, while 7-bromo-1,7-octadien-3-ol with piperidine

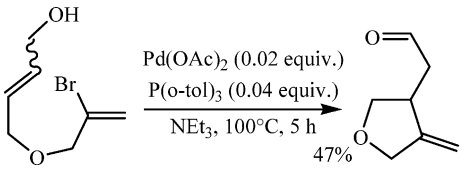


Scheme 7.



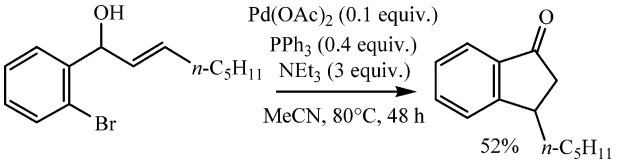
Scheme 8.

as base produced 2-methyl-3-(piperidinomethyl)-2-cyclohexenol.[106]



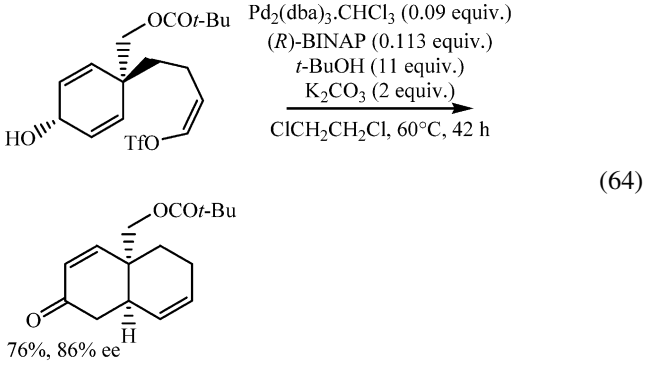
(61)

In carrying out the cyclisation of a series of vinyl bromides and aryl halides possessing an allylic alcohol moiety, Gaudin has observed that the reaction proceeds via 5-*endo*-trig rather than 4-*exo*-trig (Eq. 62), 6-*exo*-trig rather than 7-*endo*-trig and, usually, 5-*exo*-trig rather than 6-*endo*-trig processes.[107] Gaudin's conclusions are in agreement with the subsequent results of Kelly et al. on the cyclisation depicted in Eq. 63, which imply a 6-*exo*-trig process, the deoxygenated tricycle being probably formed via an intramolecular π-allyl substitution reaction.[108]



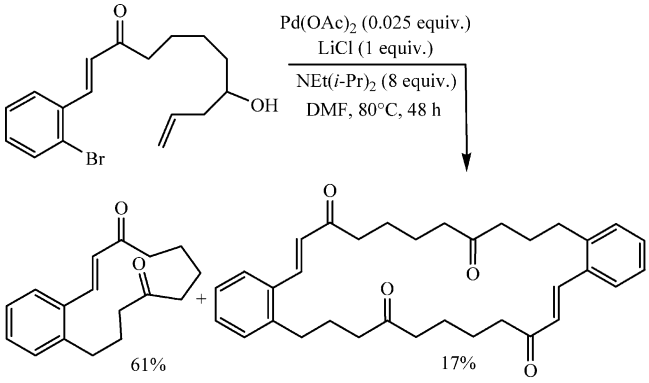
(62)

The asymmetric intramolecular Heck reaction of a vinyl triflate with a cyclohexadienic alcohol moiety has led to a key intermediate in the synthesis of vernolepin (Eq. 64).[109,110] The addition of *t*-BuOH to the reactive mixture prevented the interaction of the hydroxyl group of the substrate with palladium, thereby suppressing its oxidation and consequently precluding the formation of side products. Modifying the stereochemistry of the C–OH carbon of the substrate led to a triene, due to the β-OH elimination (Scheme 8).[110]



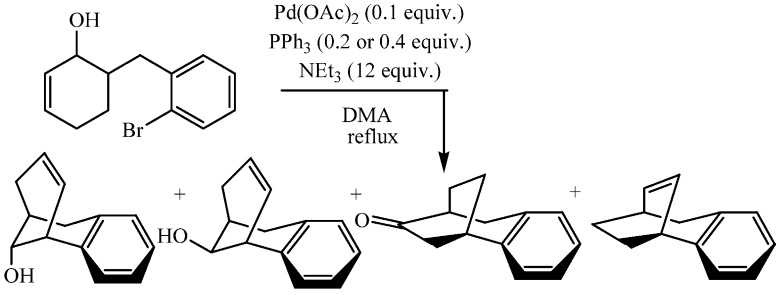
(64)

A functionalised macrocycle obtained by the intramolecular arylation of a homoallylic alcohol moiety has been used by Dyker et al. for the synthesis of a steroid framework (Eq. 65).[111]



(65)

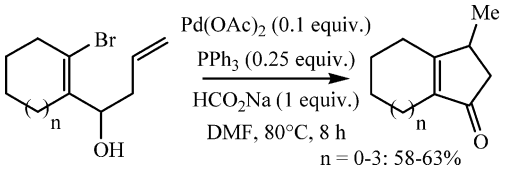
Ray et al. have synthesized cyclopentenone derivatives from 1-bromohexa-1,5-dien-3-ols in the presence of a stoichiometric amount of sodium formate (Eq. 66).[112] According to the original report, one possible mechanism would involve the intramolecular hydride transfer of the hydrogen *gem* to the hydroxy group to vinylPdBr (Scheme 9, path *a*). Some



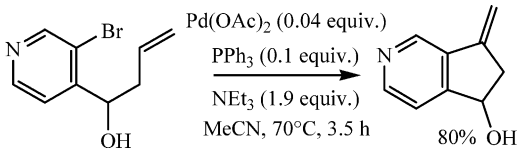
(63)

PPh_3 (0.2 equiv.), %:	49	21	14	13
PPh_3 (0.4 equiv.), %:	50	26	15	5

correspondence with the authors and the obtaining by Ray et al. of the same cyclopentenone using a substrate with a terminal triple bond instead of the double bond[113] have led to the proposition of mechanisms involving a hydride transfer from HCOONa (Scheme 9, paths *b* or *c*). Under more usual Heck reaction conditions, the 5-*exo*-trig cyclisation of another bromo homoallylic alcohol, 3-bromo-4-(1′-hydroxy-3′-butenyl)pyridine, was observed without migration of the double bond (Eq. 67).[114]

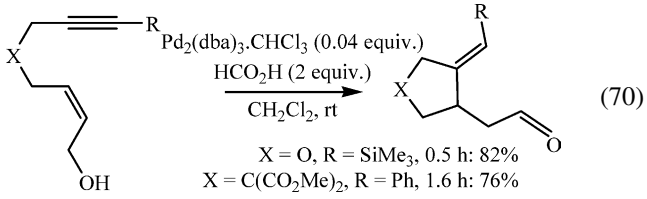


(66)

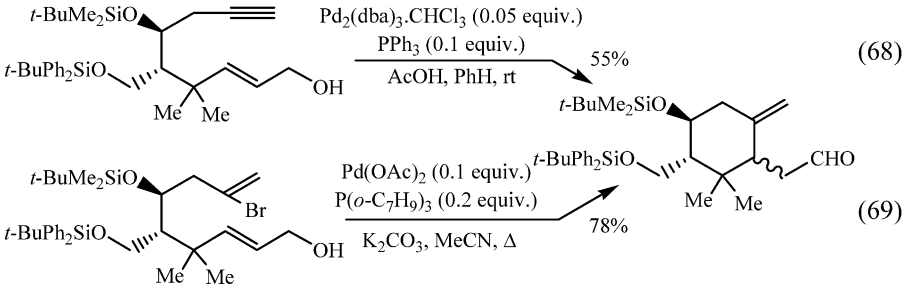


(67)

Pd[0],[116,117] the insertion of the triple bond into the H–Pd bond providing the vinylPdOAc intermediate, which would mediate the intramolecular Heck reaction to afford the σ-alkylpalladium intermediate, which undergoes a β-H elimination leading to the aldehyde.[118] In agreement with this mechanism, the same γ,δ-enal was obtained from a substrate bearing a vinyl bromide moiety instead of a triple bond (Eq. 69).[115] Recently, Müller et al. obtained similar cycloisomerisations using HCO_2H instead of $MeCO_2H$ (Eq. 70).[119–121] Under Trost's experimental conditions, the formation of the carbonyl compound could be restricted to enynes having a primary alcohol, since 1,6-enynes with a secondary hydroxy group led to the corresponding dienic alcohols (Eq. 71).[69]



(70)

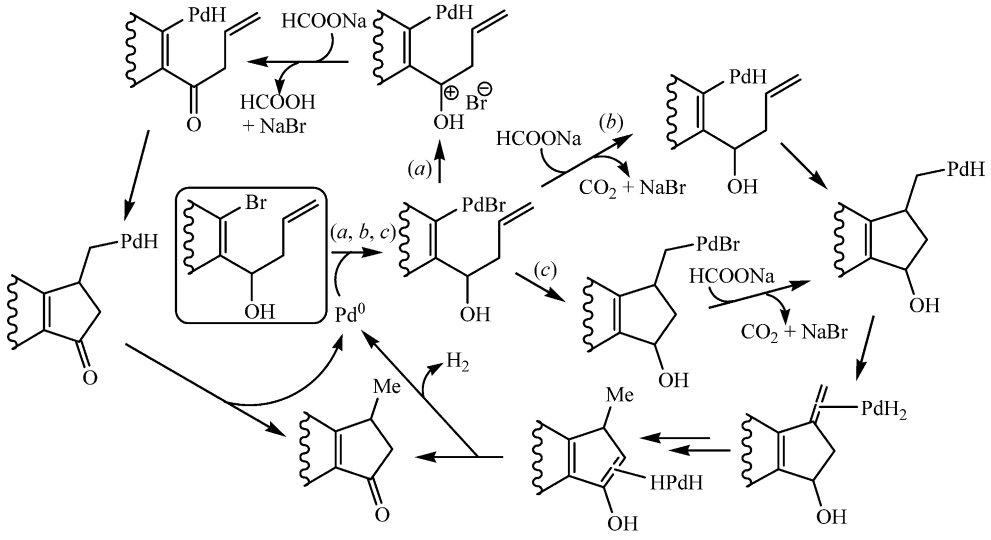


(68)

(69)

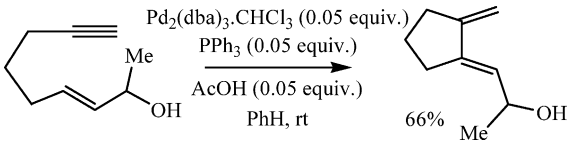
Trost et al. have reported the cyclisation depicted in Eq. 68, which has some similarity with the Heck reaction.[115] Indeed, the catalytically active species would be $HPd(OAc)L_n$ arising from the addition of AcOH to

Instead of the above Pd^0/RCO_2H systems, Lu et al. used a Pd^{II}/LiCl system to mediate a cyclisation which is also related to the Heck reaction (Eq. 72). The vinyl–Pd bond formed by chloropalladation of the triple bond inserts into

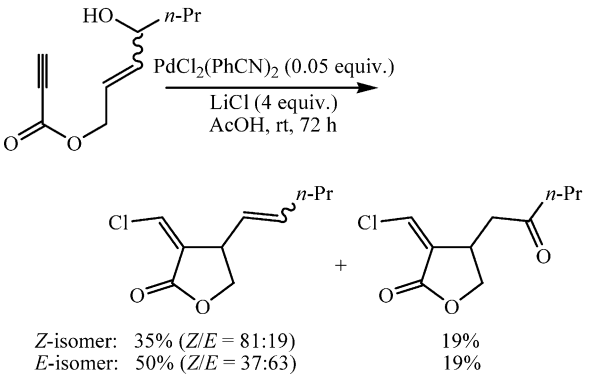


Scheme 9.

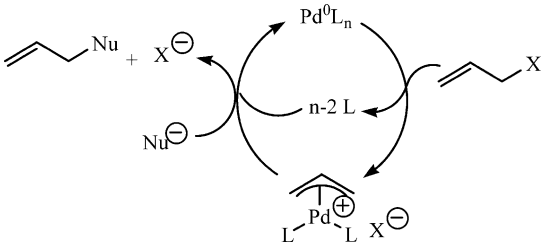
the C=C bond to afford the σ-alkylpalladium intermediate, which undergoes a β-OH or β-H elimination to deliver the two final products, the palladium hydroxide elimination occurring mainly from the antiperiplanar arrangement of hydroxide and palladium.[122]



(71)



(72)



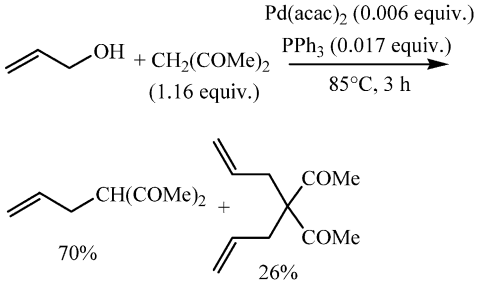
Scheme 10.

3. η^3-Allylpalladium intermediates

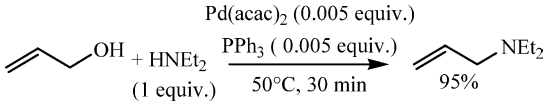
3.1. Nucleophilic additions

The well known Tsuji–Trost reaction (Scheme 10) is most often carried out from allylic esters or carbonates of organic acids, rather than from allylic alcohols, because the hydroxy is a poor leaving group. Pd-catalysed nucleophilic additions to 4-acetoxy-2-buten-1-ol-type compounds provide exclusively the substitution of the acetoxy group[2a,123] and hydroxy was not included in the list published in 1984 of allylic substituents that succumb to Pd^0 catalysts.[124]

Nevertheless, as early as 1970, Atkins et al. disclosed the Pd-catalysed reaction of allylic alcohols with acetylacetone (Eq. 73), diethylamine (Eq. 74), *n*-butylamine, phenylacetone and phenylacetonitrile at 50–85 °C in the absence of base and solvent,[125] the reaction being explained by the formation of cationic η^3-allylpalladium intermediates,[126] deprotonation of the reagent by the hydroxide counteranion and then addition. The high degree of interest of this procedure, especially in the context of the 'Green Chemistry', is the use of a starting material, an allylic alcohol, more easily available than the corresponding ester or carbonate, and the formation of only water as the byproduct.

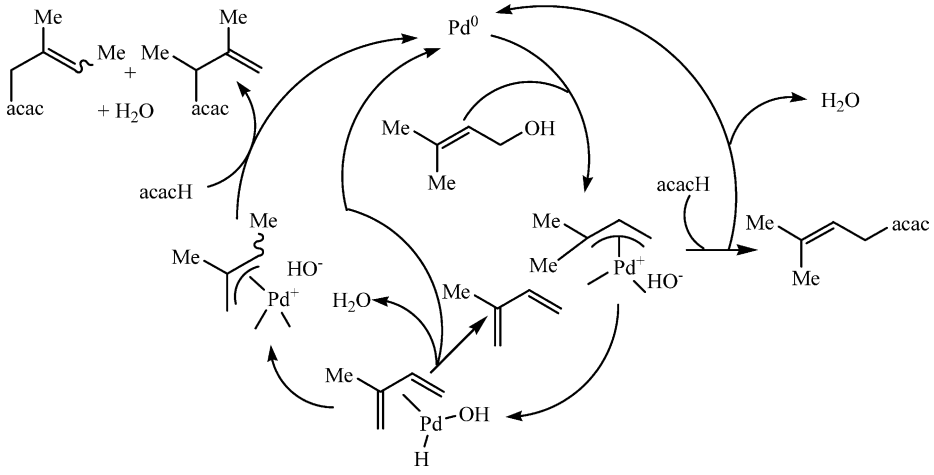


(73)



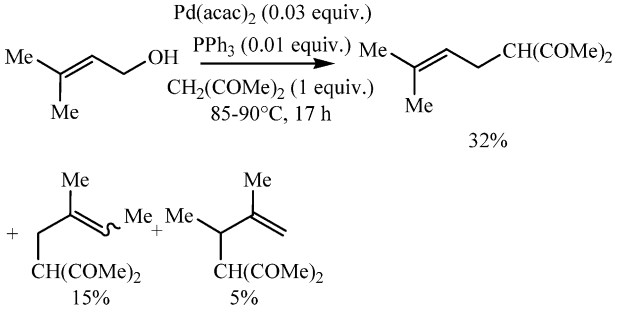
(74)

Using the Atkins' procedure, Moreno-Mañas et al. have alkylated pentane-2,4-dione with various allylic alcohols



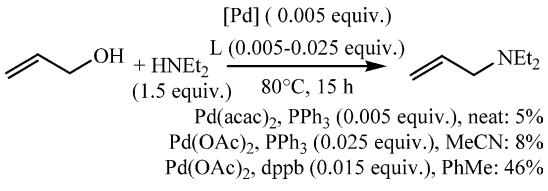
Scheme 11.

and have observed unexpected results with 3-methyl-2-buten-1-ol, since rearrangement adducts were also produced (Eq. 75). The presence of these adducts was due to the in situ formation of isoprene (Scheme 11), which was effectively detected using a Peligot tube fitted to the top of the reflux condenser and containing a solution of bromine in CCl_4.[128]

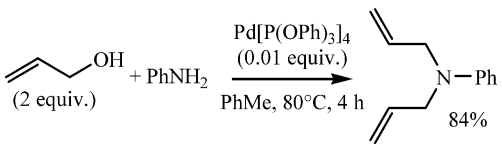


(75)

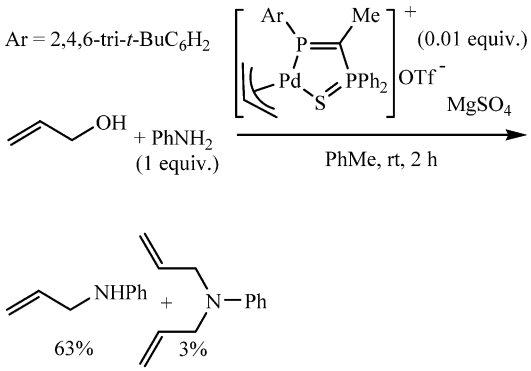
The teams of Bäckvall[129] and Mortreux[130] have been unable to reproduce Atkins' results mentioned above for the allylation of diethylamine (Eq. 74), while Masuyama et al. reported the failure of the Pd-catalysed allylation of diethylamine in the absence of promoters.[131] Furthermore, Bergbreiter et al. obtained only 5% yield for the allylation of piperidine by allyl alcohol using a heterogeneous polystyrene-bound palladium catalyst at 100 °C under neat conditions,[132] while Tanigawa et al. mentioned the lack of reactivity of diethylamine towards cinnamyl alcohol using $Pd(PPh_3)_4$ in THF at room temperature.[133] In modifying Atkins' original Pd-catalysed conditions, Mortreux et al. were unable to obtain more than 46% yield in the allylation of diethylamine (Eq. 76).[130] Nevertheless, palladium-catalysed procedures for the allylation of amines,[134] amides,[135,136] sulfonamides[136,137] and imides[138] by allyl alcohol have been reported in the Japanese literature and patents. Recent papers have reported the effective allylation of aniline using either $Pd[P(OPh)_3]_4$ (Eq. 77)[139] or cationic Pd catalysts (Eq. 78),[127d,140,141] and, interestingly, a similar allylation has been carried out with an optically active allylic alcohol without loss of optical purity (Eq. 79).[140]



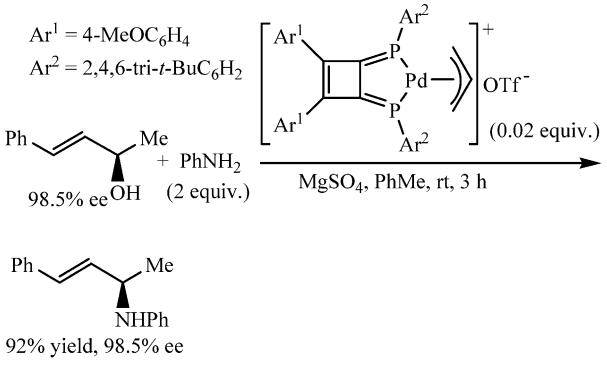
(76)



(77)

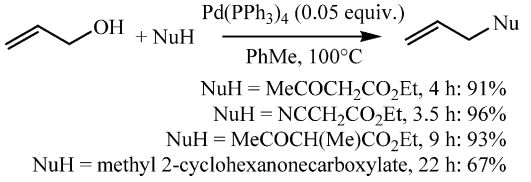


(78)

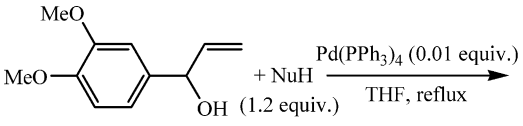


(79)

Although either preformed anionic species[142] or the addition of some base[128,143] were sometimes used, even with simple allylic alcohols, the effective allylation of active methylene compounds has been achieved at 80–100 °C in the absence of any base or additive using an organic solvent at 80–100 °C with $Pd(PPh_3)_4$ (Eqs. 80 and 81),[144–146] a polyethylene-bound soluble recoverable Pd^0 catalyst (tetrakis[polyethylenediphenylphosphine]palladium),[147] $Pd(OAc)_2/PPh_3$ (Eq. 82),[130,148] $Pd(OAc)_2$/dppb,[130] $Pd[P(OPh)_3]_4$,[139,149] or in the absence of solvent at 50 °C with cationic Pd catalysts (Eq. 83).[127d,140] In contrast, Tsuji et al. obtained no more than 8% yield using the $Pd_2(dba)_3 \cdot CHCl_3/PPh_3$ catalytic system in THF at 65 °C for the allylation of methyl 2-methyl-3-oxopentanoate by allyl alcohol,[150] and the Moreno-Mañas team has observed a low reactivity of allylic alcohols having an additional double bond, no transformation of geraniol being obtained in the absence of an added base.[128]

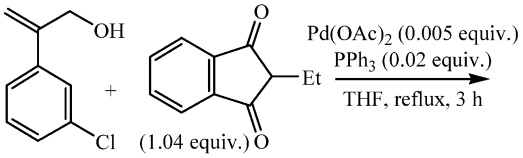


(80)

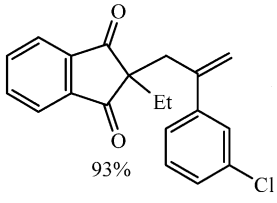


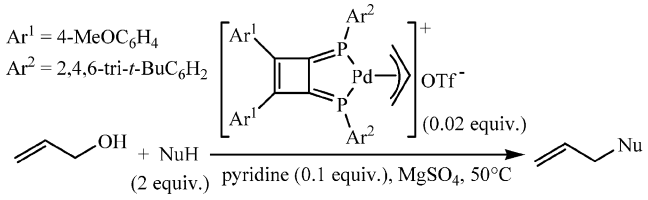
NuH: 2-methyl-1,3-cyclopentanedione (98%), 2,4-pentanedione (99%), methyl acetoacetate (99%), diethyl malonate (81%)

(81)



(82)

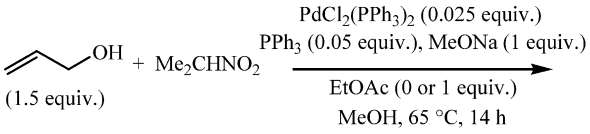


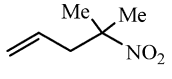


NuH = $MeCOCH_2CO_2Et$, 3 h: 92%, NuH = $EtO_2CCH_2CO_2Et$, 12 h: 92%
NuH = ethyl 2-cyclohexanonecarboxylate, 12 h: 95%

(83)

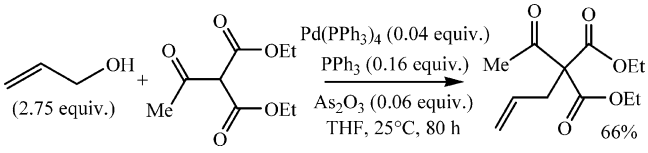
The alkylation of allylic alcohols with aliphatic nitrocompounds carried out in a basic medium was more efficient in the presence of a stoichiometric amount of ethyl acetate (Eq. 84).[151] Aleksandrowicz et al. assumed that this ester acts as a hydroxy-anion scavenger, replacing the strong nucleophile OH^- by the weak nucleophile AcO^-, thus eliminating the competitive addition between OH^- and the anion derived from the nitroalkane to the cationic η^3-allylpalladium intermediate. We suggest another possibility for the role of the ethyl acetate, namely the in situ esterification of the alcohol, as has been reported for the effective copper-mediated alkylations of allylic alcohols;[152] this would facilitate the formation of the η^3-allylpalladium intermediate. In fact, Trost et al. have envisaged that the Pd-catalysed substitution of 1-(1′-hydroxyethyl)cyclopentene with the sodium enolate of dimethyl malonate involves firstly transesterification, leading to the corresponding unsymmetric diester.[142] After all, various procedures have been proposed to activate allylic alcohols and, in particular, their in situ transformation into esters of inorganic acids using arsenic^{III} oxide (Eq. 85)[153,154] or boric oxide (Eq. 86).[155,156] Moreover, Kočovský et al. have reported the Pd-catalysed substitution of various allylic alkoxides (M = B, Mg or Al).[157]



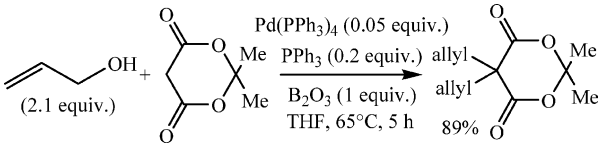


without EtOAc: 36%
with EtOAc: 68%

(84)

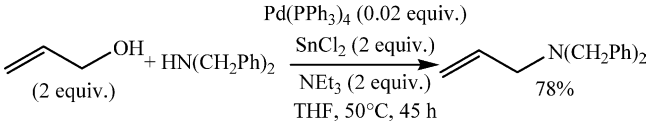


(85)

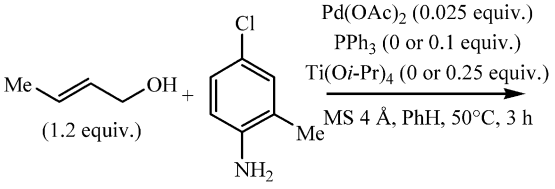


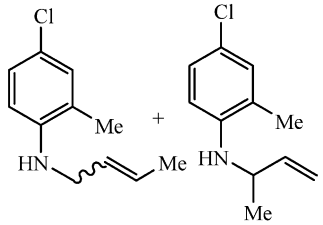
(86)

In order to activate the allylation of amines, Masuyama et al. have used tin^{II} chloride (Eq. 87),[131] while Yang et al. have intensively developed the use of titanium^{IV} isopropoxide (Eq. 88),[158–161] and applied their procedure to the synthesis of heterocycles from (*Z*)-2-buten-1,4-diol and 2-aminophenols or *o*-phenylenediamines (Eqs. 89 and 90).[159,160] Masuyama et al. suggested that $SnCl_2$ promotes the formation of the η^3-allylpalladium, while Yang et al. suspected an allylic titanate formed by an exchange reaction of the allylic alcohol with Ti(O*i*-Pr)$_4$, this allylic titanate leading to the η^3-allylpalladium intermediate.



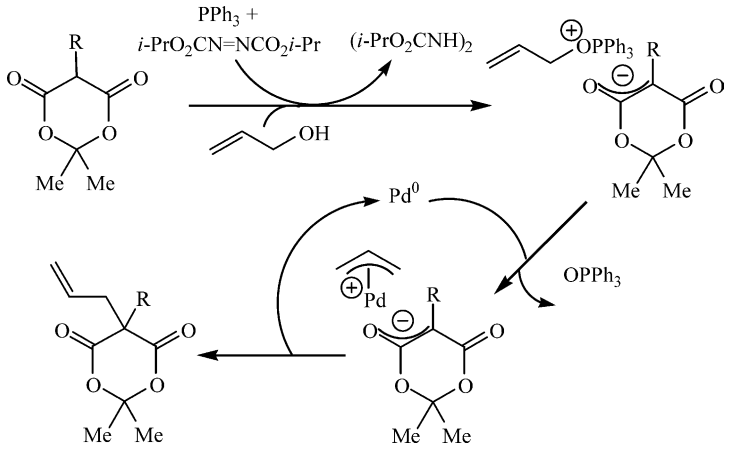
(87)



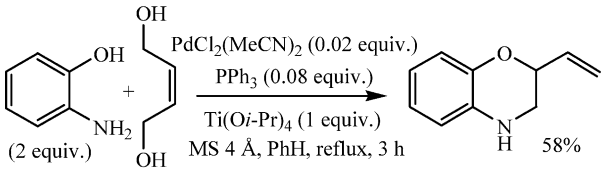


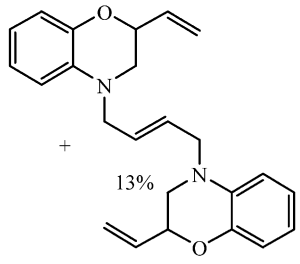
without PPh_3 or Ti(O*i*-Pr)$_4$:	0%	0%
with PPh_3 and Ti(O*i*-Pr)$_4$:	44%	36%

(88)

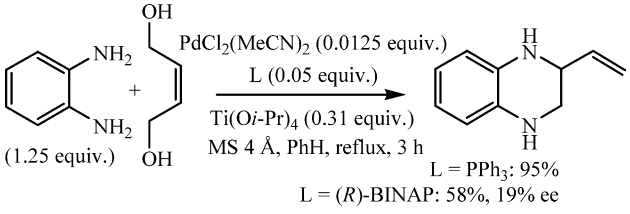


Scheme 12.

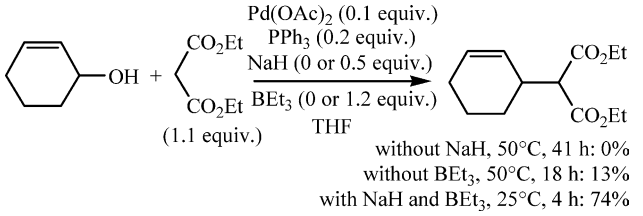




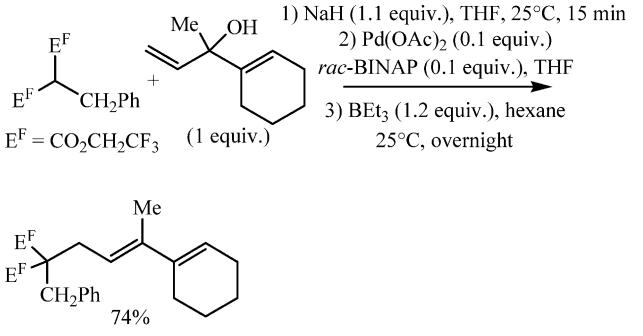
(89)



(90)

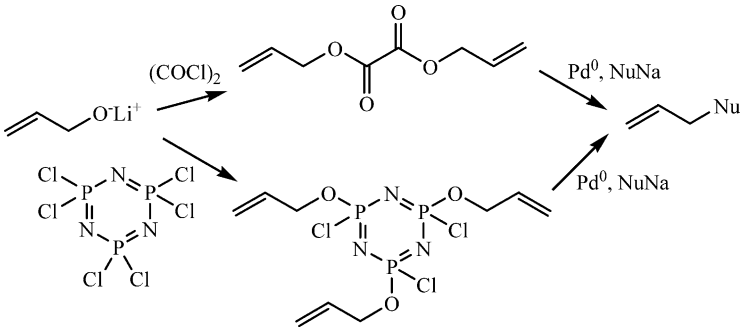


(91)



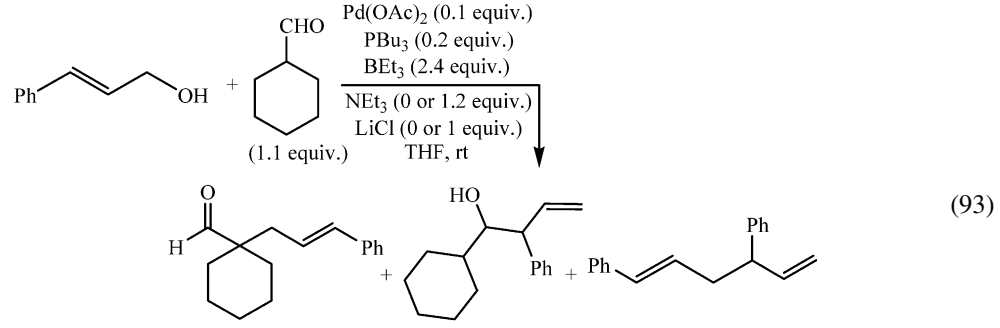
(92)

Triethylborane has been used as additive for the allylation of active methylene and methine compounds (Eqs. 91 and 92)[162–164] and, according to Tamaru et al., who have intensively studied this procedure, the first step would be the coordination of the hydroxy group to the boron species, with possibly the formation of the corresponding diethyl borate.[163] Reacting aldehydes with allylic alcohols using



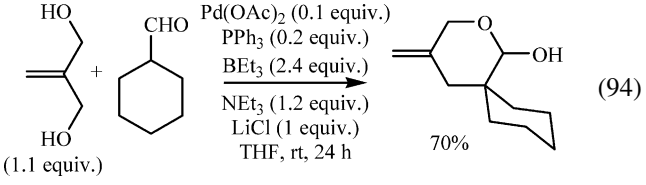
Scheme 13.

this method led to an unselective reaction, but with triethylamine and lithium chloride as additional additives, the α-allylation of the aldehyde has been carried out with a high yield (Eq. 93);[165] the use of these additives with 2-hydroxymethyl-2-propen-1-ol as allylating agent led to cyclic hemiacetals (Eq. 94).[166]



(93)

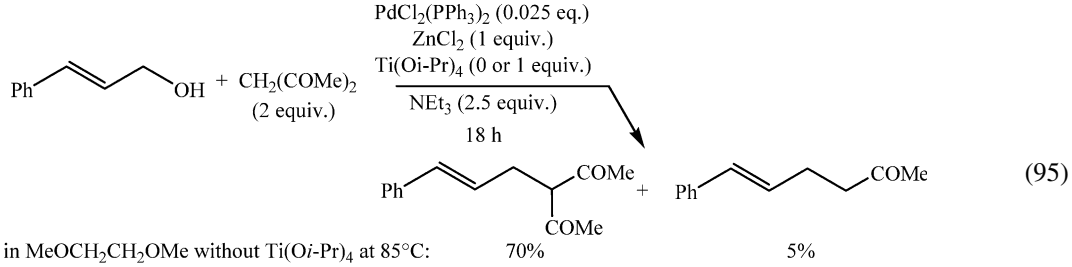
without NEt_3 and LiCl, 4 h:	30%	39%	20%
with NEt_3, 18 h:	70%	23%	0%
with NEt_3 and LiCl, 40 h:	92%	4%	0%



(94)

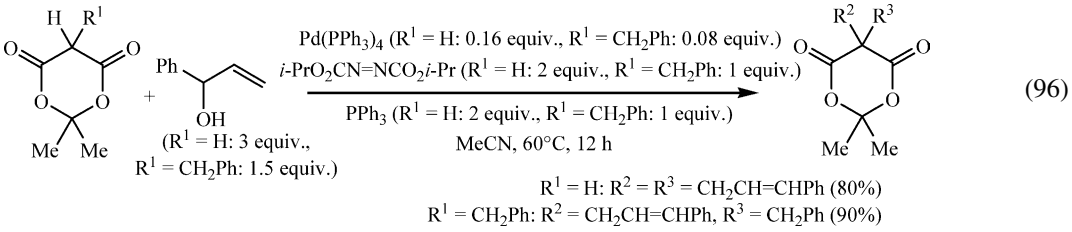
by Pd^0 catalysis (Eq. 96) and Shing et al. have proposed the intermediates depicted in Scheme 12.[168]

Vankar et al. have used oxalyl chloride and hexachlorotriphosphazene (HCP) to activate the allylation of dimethyl malonate (Eq. 97). Substoichiometric amounts of these activators are sufficient, since they are able to activate two to three molecules of the allylic alcohol (Scheme 13) and the method allows a chirality transfer.[169]



(95)

in $MeOCH_2CH_2OMe$ without $Ti(O\textit{i}\text{-}Pr)_4$ at 85°C:	70%	5%
in $(MeOCH_2CH_2)_2O$ with $Ti(O\textit{i}\text{-}Pr)_4$ at 120°C:	0%	70%



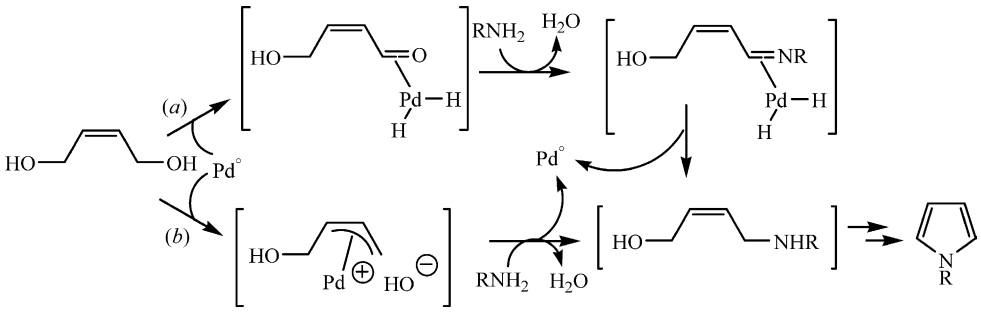
(96)

Miura et al. have used zinc chloride as an additive for the addition of acetylacetone to allylic alcohols (Eq. 95). Under these conditions, the nucleophilic species would be zinc acetylacetonate (see Eq. 106 below) and a small amount quantity of the monoketone was also produced. This side product became the main adduct with titanium^{IV} isopropoxide as an additional additive (Eq. 95) and it has been established that the deacetylation is due to a subsequent reaction of the diketone mediated by $Ti(O\textit{i}\text{-}Pr)_4$.[167] This procedure was also effective for the addition of dibenzoylmethane, diethyl malonate and ethyl benzoylacetate, while ethyl acetoacetate led to a complex mixture.[167]

The *C*-alkylations of Meldrum acids with secondary allylic alcohols under Mitsunobu conditions have been improved

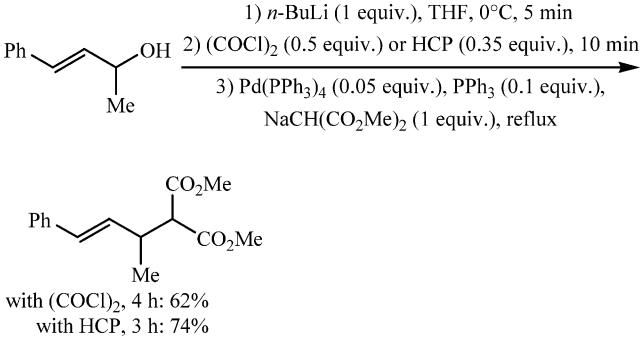
Carbon dioxide has been used to promote the addition of diethylamine (Eq. 98)[170,171] and active methylene compounds[171] to allylic alcohols; the promotion effect would be due to the formation of the allylic hydrogencarbonate.[171]

The synthesis of *N*-substituted pyrroles from (*Z*)-2-buten-1,4-diol and primary amines (Eq. 99) has been explained by the formation of 4-alkylaminobut-2-en-1-ols as intermediates, the first step of the cascade reaction being the

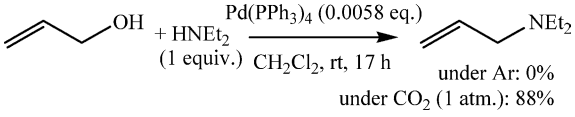


Scheme 14.

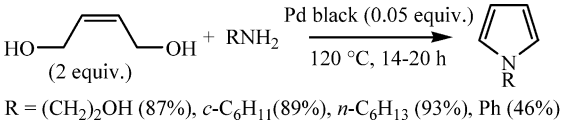
dehydrogenation of one hydroxy group (Scheme 14, path *a*).[172] From the Atkins' report[125] and the subsequent studies summarised above, we suggest the nucleophilic addition of the amine to a cationic η^3-allylpalladium complex (Scheme 14, path *b*) as another possibility for the formation of this intermediate.



(97)



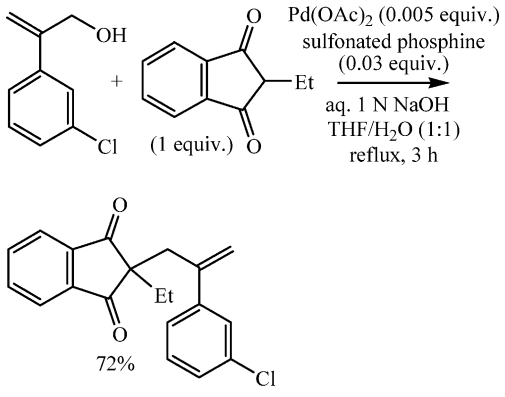
(98)



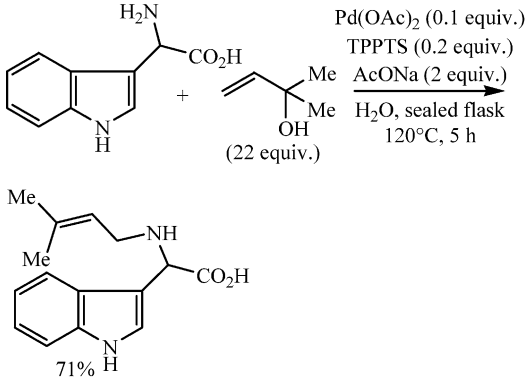
(99)

A few research teams have studied the Pd-catalysed nucleophilic additions to allylic alcohols in aqueous media.[148,173–179]

The coupling of 2-ethylindan-1,3-dione with 2-(3-chlorophenyl)prop-2-en-1-ol (Eq. 100) has been performed at reflux in a water–THF mixture containing a water-soluble sulfonated triphenylphosphine, PPh_3-$(SO_3H)_n$ ($n=1$–3) and, interestingly, the aqueous layer was recycled with a low decrease of the chemical yield.[148] The well-known similarly soluble ligand, TPPTS, was used for the regioselective *N*-allylation of indole derivatives in water (Eq. 101).[173,174]

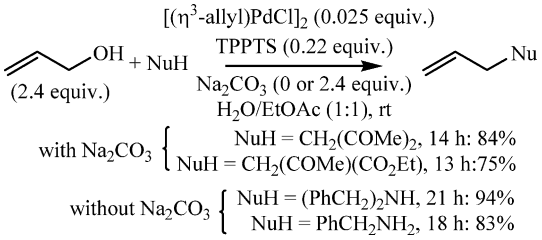


(100)



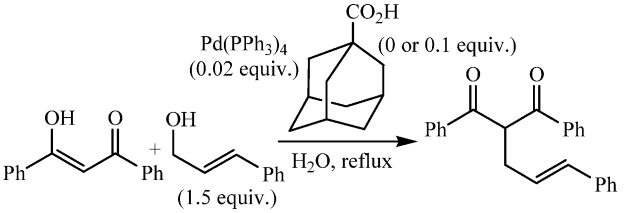
(101)

Recently, Oshima et al. disclosed that a combination of $[(\eta^3\text{-allyl})_2PdCl]_2$ and TPPTS was highly effective for room temperature C–C and C–N bond formation from hydrophilic allylic alcohols (Eq. 102), no reaction being observed with a hydrophobic substrate such as cinnamyl alcohol. Although usually carried out in the presence of Na_2CO_3 and in H_2O/EtOAc, the process takes place also under neutral conditions and in H_2O/Et_2O, thus excluding an activator role of CO_2 from Na_2CO_3 and the involvement of allylic acetate via the transesterification with EtOAc. Theoretical calculations have led to the assumption that the generation of the η^3-allylpalladium intermediate is facilitated by the hydration of the hydroxy group of the allylic alcohol. The requirement for substrates with hydrophilic properties allows the selective monoamination of (*Z*)-2-butene-1,4-diol and 2-(hydroxymethyl)prop-2-en-1-ol with dibenzylamine, the substitution of one hydroxy group leading to a hydrophobic compound.[179]



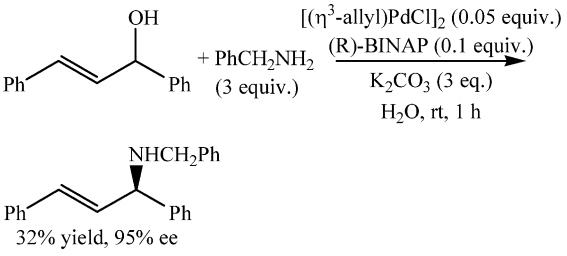
(102)

Instead of the combination of a Pd catalyst and a water-soluble phosphine, Kobayashi et al. used a combination of catalytic amounts of both $Pd(PPh_3)_4$ and a carboxylic acid, in particular 1-adamantanecarboxylic acid, to perform the effective reaction of various carbon nucleophiles with allylic alcohols in water (Eq. 103).[176,177] As a key role of the carboxylic acid is to accelerate the reaction, the authors propose the catalytic cycle depicted in Scheme 15, where the counteranion of the cationic η^3-allylpalladium intermediate is the carboxylate.[176] Subsequently, Yamamoto et al. have reported a similar procedure, but under neat conditions and with acetic acid rather than 1-adamantanecarboxylic acid.[178] According to both teams, the dramatic effect of the carboxylic acid additive is not observed in toluene or dioxane.



(103)

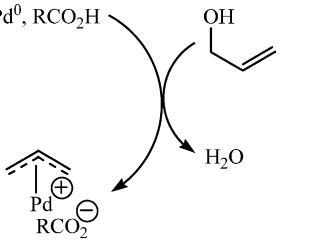
Amination in water has also been carried out without a water-soluble phosphine or a carboxylic acid as additive, but the yield was low, as reported by Sinou's group, which has studied the enantioselective amination of 1,3-diphenylprop-2-en-1-ol under such conditions, a high enantiomeric excess being nevertheless obtained using (*R*)-BINAP as the ligand (Eq. 104).[175]



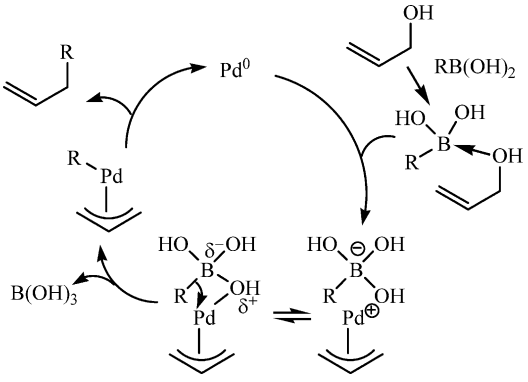
(104)

The literature also contains examples of Pd-catalysed C–C bond formation from the reaction of unsaturated alcohols with organometallic complexes.

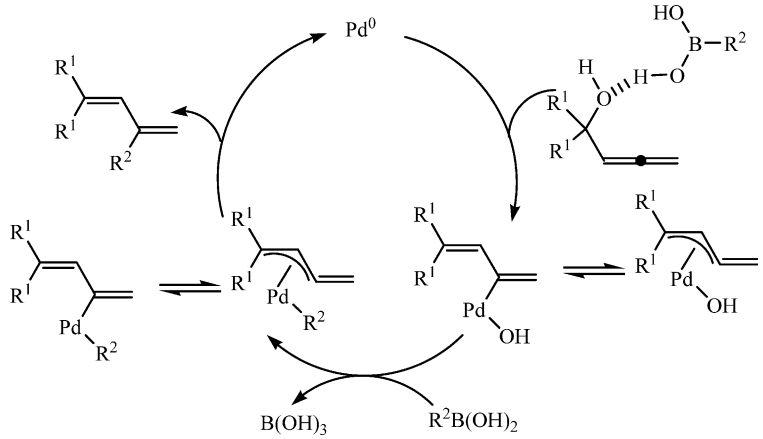
Grignard reagents have been coupled with allylic alcohols (Eq. 105) through a reaction which would involve an



Scheme 15.

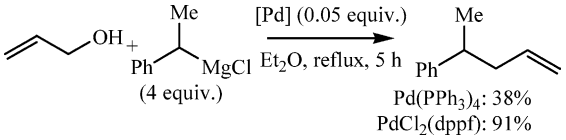


Scheme 16.



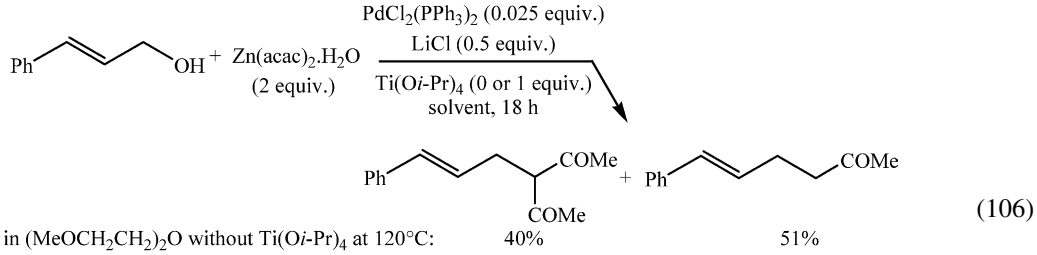
Scheme 17.

(η^3-allyl)(aryl or alkyl)palladium complex as the key intermediate.[180,181]



(105)

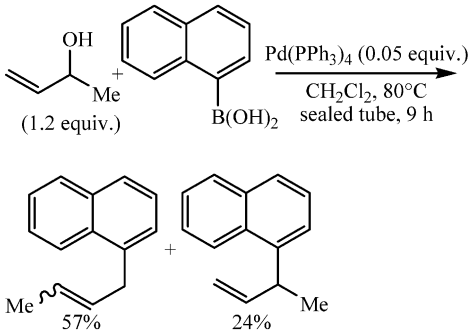
Zinc acetylacetonate added to allylic alcohols in the presence of lithium chloride and a palladium catalyst (Eq. 106). As above (Eq. 95), the reaction carried out with Ti(O*i*-Pr)$_4$ as additive led to mono-deacetylation of the adduct (Eq. 106).[167]



in $(MeOCH_2CH_2)_2O$ without Ti(O*i*-Pr)$_4$ at 120°C:	40%	51%
in $MeOCH_2CH_2OMe$ without Ti(O*i*-Pr)$_4$ at 85°C:	85%	7%
in $(MeOCH_2CH_2)_2O$ with Ti(O*i*-Pr)$_4$ at 120°C:	0%	85%

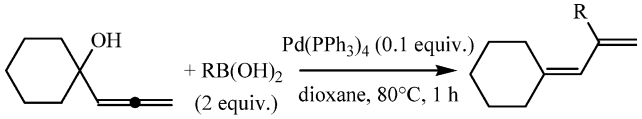
(106)

Recently, Tsukamoto et al. have disclosed the cross coupling of allylic alcohols with aryl- and vinylboronic acids (Eq. 107) and presumed that the oxidative addition of the allylic alcohol to Pd^0 species is facilitated by coordination with $RB(OH)_2$ (R=Ar, R'CH=CH_2), as depicted in Scheme 16.[182] Subsequently, Ikariya el al. have assumed that the 1:1 mixture of $Pd_2(dba)_3CHCl_3$ and $P(OPh)_3$ is the best catalytic system, and they have obtained the quantitative formation of *p*-allylacetophenone from the coupling of allyl alcohol with *p*-acetylphenylboronic acid.[183]



(107)

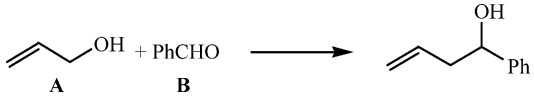
With primary, secondary or tertiary allenic alcohols as substrates, the group of Yoshida and Ihara has reported that the coupling with aryl- or alkenylboronic acids led to substituted dienes (Eq. 108).[184] The increased leaving group ability of the allenic hydroxy group by interaction with the boronic acid would facilitate the formation of the allylpalladium, which would evolve towards the substituted adduct, as depicted in Scheme 17.[185]



R = Ph (83%), *o*-MeC_6H_4 (99%), *p*-$AcOC_6H_4$ (67%), 1-hexenyl (84%)

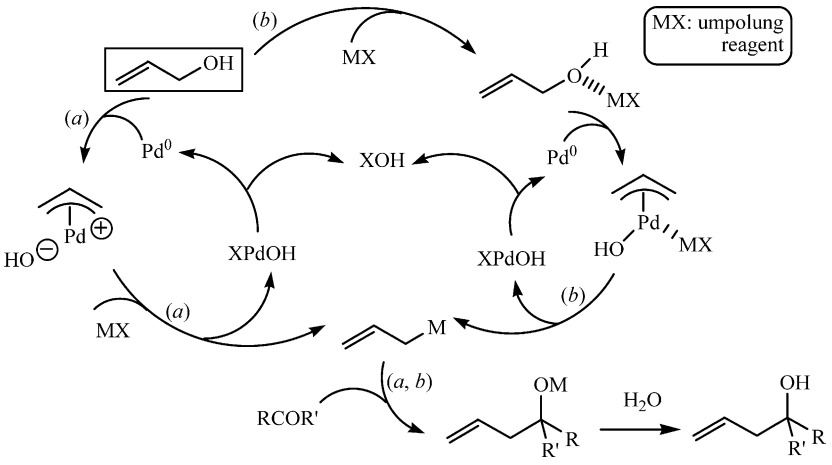
(108)

Table 2. Allylation of benzaldehyde



[**A**:**B**]	Catalyst (equiv)	Umpolung reagent (equiv)	Solvent	*t* (°C)	Time (h)	Yield (%)
[≥3:2][189]	$PdCl_2(PhCN)_2$ (0.02)	$SnCl_2$ (3)	THF	25	24	83
[2:1][195]	$PdCl_2$ (0.05)	$SnCl_2$ (2)	H_2O/THF (1:4)	rt	16	95
[2:1][195]	$PdCl_2$ (0.05)	$SnCl_2$ (2)	H_2O/THF (2:3)	rt	16	62
[2:1][195]	$PdCl_2$ (0.05)	$SnCl_2$ (2)	H_2O	rt	16	29
[2:1][194]	$PdCl_2(TPPMS)_2$[a] (0.01)	$SnCl_2$ (3)	H_2O/heptane (1:1)	35	7	98
[1:1.2][198]	$Pd(OAc)_2/PPh_3$ (0.05/0.1)	BEt_3 (2.4)	THF	25	28	64
[2:1][199]	$Pd(PPh_3)_4$ (0.05)	InI (2)	THF	rt	13	76
[2:1][200]	$Pd(OAc)_2$ (0.1) TPPTS (0.5)	InBr (2)	H_2O	rt	4.5	100
[3:1][201]	$Pd(PPh_3)_4$ (0.02)	In (2), $InCl_3$ (0.5)	THF	rt	20	12
[3:1][201]	$Pd(PPh_3)_4$ (0.02)	In (2), CuCl (1)	H_2O	50	44	62
[3:1][201]	$Pd(PPh_3)_4$ (0.02)	In (2), $InCl_3$ (0.5)	H_2O/THF (1:1)	rt	20	94
[3:1][201]	$Pd(PPh_3)_4$ (0.02)	In (2), $FeCl_3$ (1)	H_2O/THF (1:1)	rt	20	87
[3:1][201]	$Pd(PPh_3)_4$ (0.02)	In (2), CuCl (1)	H_2O/THF (1:1)	rt	20	86
[3:1][201]	$Pd(PPh_3)_4$ (0.02)	In (2), $SnCl_2$ (1)	H_2O/THF (1:1)	rt	20	5

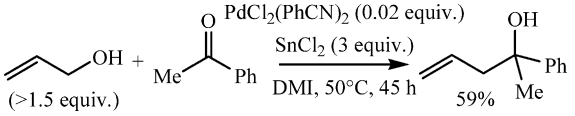
[a] TPPMS, (*m*-$NaOSO_2C_6H_4$)PPh_2.



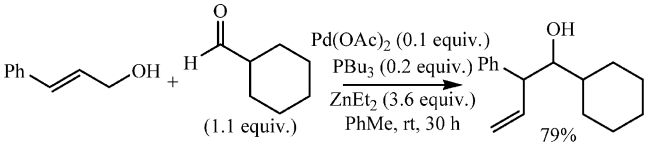
Scheme 18.

3.2. Electrophilic additions

The reactions described in this section involve the umpolung concept, that is, reactions where the electrophilic η^3-allylpalladium intermediate is converted into a nucleophilic species by transmetallation.[186] In this way, the allylation of aldehydes and ketones by allylic alcohols in the presence of Pd catalysts has been mediated by $SnCl_2$,[187–196] $ZnEt_2$,[197] BEt_3,[166,198] InI,[199] InBr,[200] or with a mixture of indium and a Lewis acid, in particular $InCl_3$[201] (Table 2; Eqs. 109 and 110). Some of these reactions have been carried out in aqueous media[194,195,200,201] and with a water-soluble phosphine ligand,[194,200] the use of TPPTS in water allowing the recycling of the catalytic system.[200]

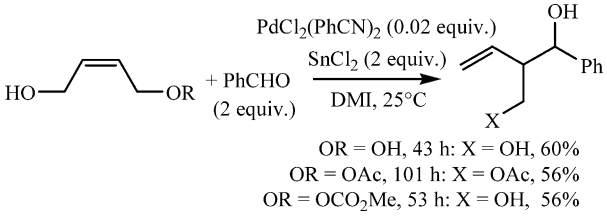


(109)

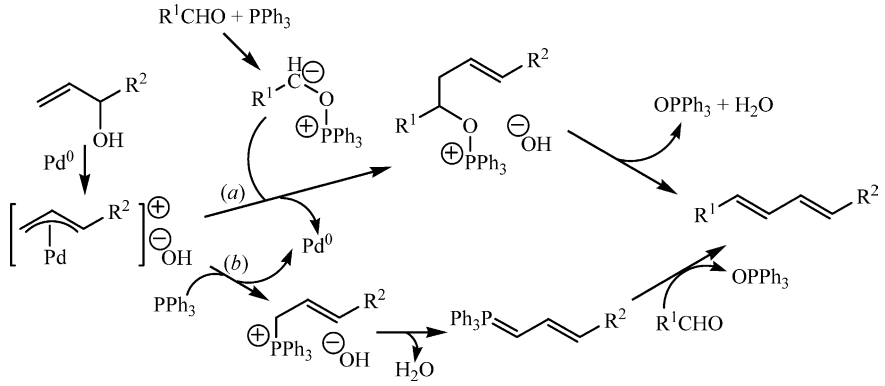


(110)

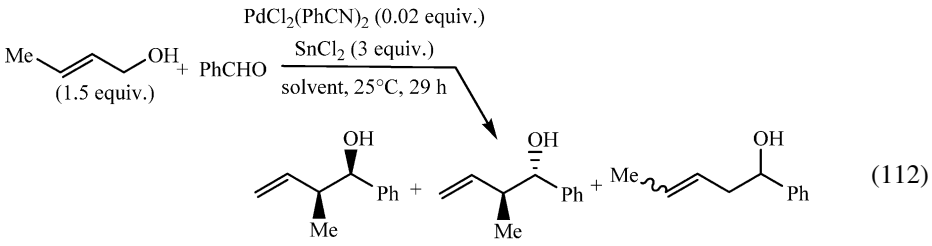
Possible mechanisms of these reactions are illustrated in Scheme 18. The activation of the substrate by the umpolung reagent (path *b*) postulated by some authors is supported by Masuyama et al., who have disclosed that, for the Pd-catalysed $SnCl_2$-mediated allylation of benzaldehyde by (*Z*)-2-buten-1,4-diol derivatives, the order of reactivity of leaving groups is $OCO_2Me > OH > OAc$ (Eq. 111).[189] Masuyama et al. suggest that the hydroxy group reacts with $SnCl_2$ to form a better leaving group than the acetoxy group[189] and they have proved the formation of allyltrichlorostannane from allyl alcohol and the $PdCl_2(PhCN)_2$/$SnCl_2$ mixture.[191] The same group has disclosed that the regio- and diastereoselection of the reaction between 2-buten-1-ol and benzaldehyde depends on the polarity of the solvent (Eq. 112[188,189,193] and is modified by ultrasound irradiation (Eq. 113).[192] The $PdCl_2(PhCN)_2$/$SnCl_2$ procedure has been used for the allylation of resin-bound aldehydes with various allylic alcohols.[195]



(111)

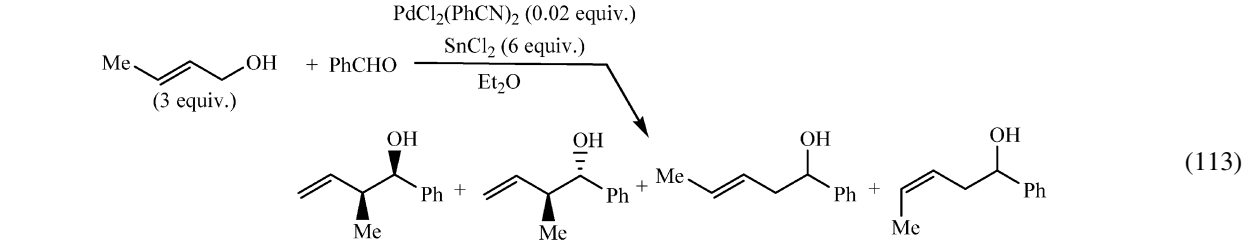


Scheme 19.



in DMI, 24 h: 75%	29	/	71	/	0	
in DMSO, 136 h: 34%	65	/	35	/	0	
in DMF, 63 h: 89%	30	/	70	/	0	
in EtOH, 72 h: 79%	38	/	41	/	21	
in THF, 25 h: 72%	22	/	25	/	53	
in DME, 142 h: 22%	41	/	3	/	56	

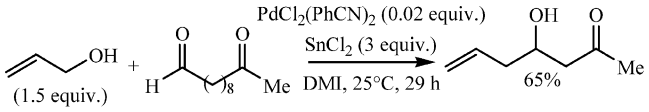
(112)



without ultrasound, rt, 72 h: 8%	4	/	4	/	57	/	35	
with ultrasound, 10-15°C, 4 h: 56%	18	/	4	/	62	/	16	

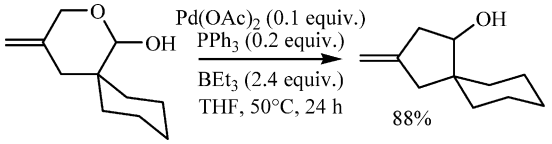
(113)

The allylation of ketones, which is slower than that of aldehydes, has allowed the chemoselective addition to a ketoaldehyde (Eq. 114).[187]

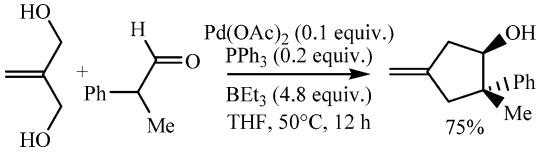


(114)

The intramolecular allylation of aldehydes leading to 3-methylenecyclopentanols has recently been reported by Tamaru et al. using the $Pd(OAc)_2/PPh_3/BEt_3$ system and the cyclic hemiacetals prepared through the Pd-catalysed reaction between an aldehyde and 2-hydroxymethyl-2-propen-1-ol depicted in Eq. 94, the intramolecular allylation taking place from the open form of the lactol (Eq. 115). In fact, the synthesis of 3-methylenecyclopentanols can be carried out directly from the bis-allyl alcohol and the aldehydes that possess the α-proton with relatively high acidity (Eq. 116).[166]

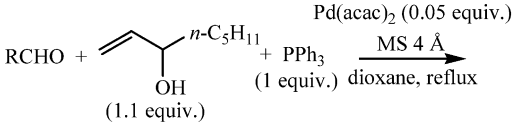


(115)

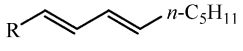


(116)

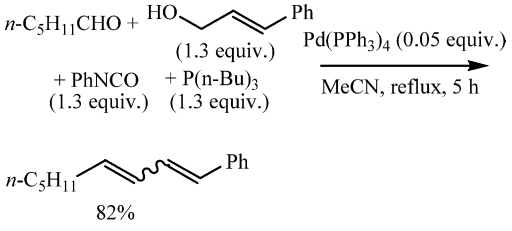
In 1981, Moreno-Mañas et al. reported the Pd-catalysed synthesis of linear 1,3-dienes from the reaction between aldehydes, triphenylphosphine and primary or secondary allylic alcohols (Eq. 117).[202–204] These authors have proposed two possible mechanistic paths, which do not involve an electrophilic addition of an allylic complex (Scheme 19),[202,203,205] and a mechanism similar to pathway *b* has been subsequently retained by Okukado et al. for the synthesis of conjugated dienes under different experimental conditions (Eq. 118), the η^3-allylpalladium intermediate arising from the in situ formed allylic phenylcarbamate.[206]



(117)



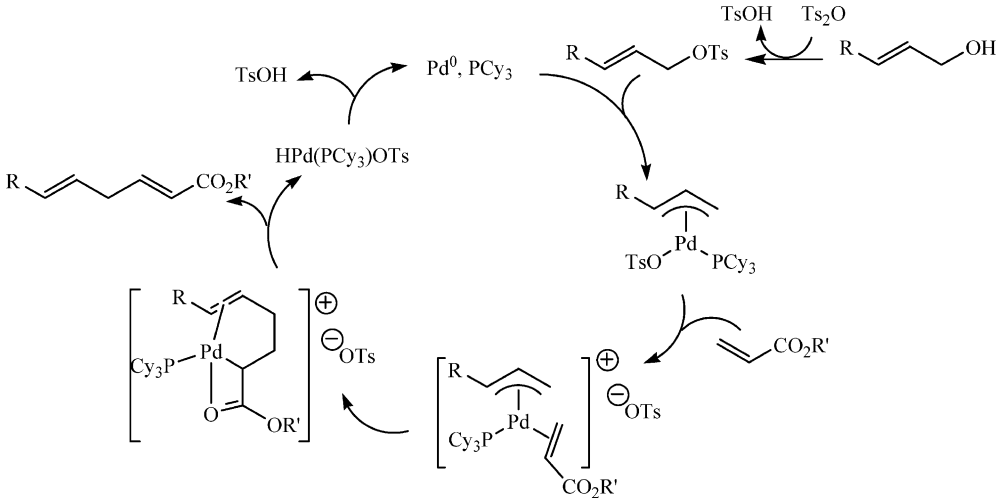
R = *p*-ClC_6H_4 (40 h: 49%), *n*-C_5H_{11} (7 d: 32%)



(118)

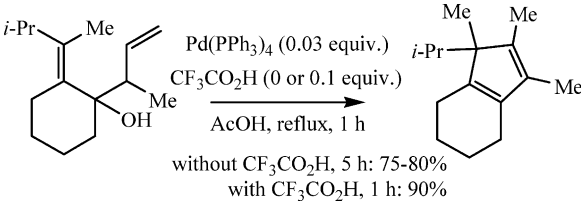
3.3. Insertion of C–C double or triple bonds

Santelli et al. have observed that the formation of cyclopentadienes via the Pd-catalysed cyclisation of 1,5-hexadien-3-ols was improved in the presence of a catalytic amount of trifluoroacetic acid (Eq. 119) and experiments using deuteriated materials have shown the complexity of the mechanism.[207] Subsequently, Tsukada et al. have coupled primary and secondary allylic alcohols with *n*-butyl acrylate in the presence of stoichiometric

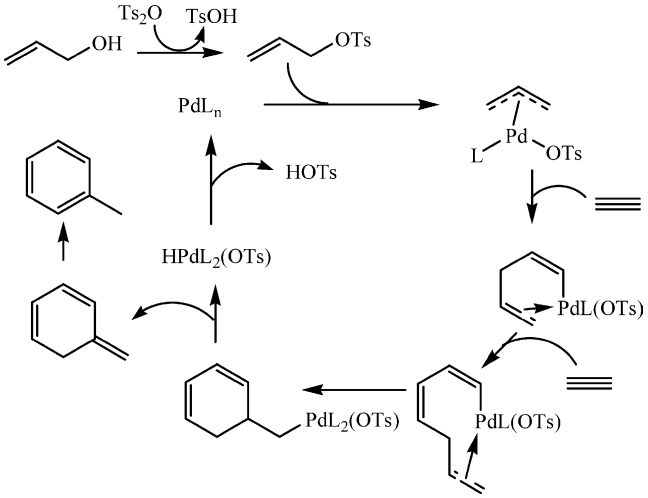


Scheme 20.

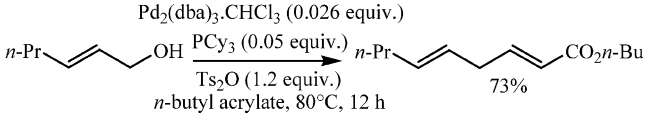
amounts of *p*-toluenesulfonic anhydride (Eq. 120).[208] The same adducts were obtained using allylic tosylates instead of allylic alcohols plus Ts_2O, and the authors proposed the mechanism depicted in Scheme 20, an η^3-allylpalladium intermediate being in agreement with a computational study reported simultaneously.[209] Tsukada et al. noted the advantage of the in situ preparation of allylic tosylates, since these compounds may have low stability. A related reaction involving a benzylpalladium instead of an allylpalladium intermediate[104] has been documented in Eq. 59.



(119)

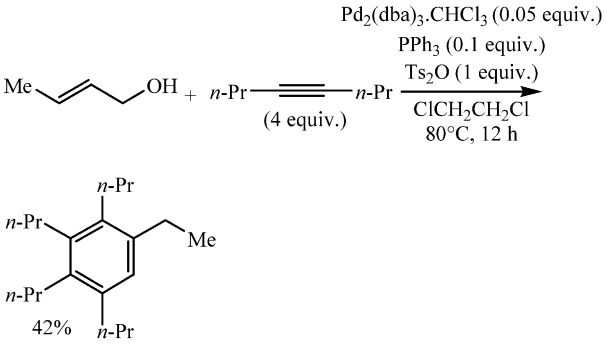


Scheme 21.

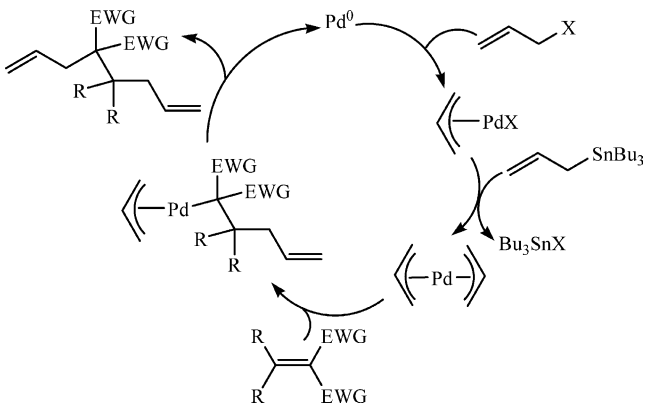


(120)

The coupling of allylic alcohols with C–C triple bonds can occur via Heck-type reactions, as documented in Section 2.2. (Eqs. 68, 70 and 71). Another reactive pathway is the benzannulation reported by Tsukada et al. (Eq. 121), which would proceed through an η^3-allylpalladium intermediate (Scheme 21)[210] obtained, as above, from the in situ generated allylic tosylate.[211]



(121)



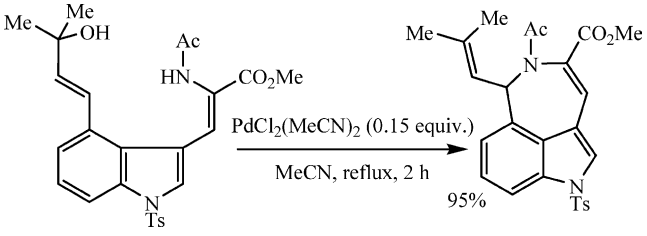
Scheme 22.

Yamamoto et al. have disclosed that the Pd-catalysed bis-allylation of activated alkenes using both allyltributylstannane and allyl-X, via a reaction occuring as shown in Scheme 22, is less effective with X=OH than X=Cl.[212,213]

4. Aminopalladation

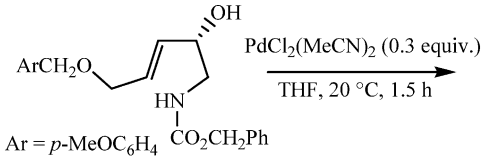
The activation of an alkene by coordination with Pd^{II} may allow the nucleophilic addition of an amine bearing a deactivating group,[214] this reaction being similar to the oxypalladation of alkenes. Such a process has been applied to the formation of azacycles by the intramolecular addition of the amino group to an allylic alcohol.

In the course of their synthesis of ergot alkaloids, Hegedus et al. carried out the intramolecular addition of an acetamido group to a tertiary allylic alcohol using $PdCl_2(MeCN)_2$ as the starting catalyst (Eq. 122).[215] According to these authors, the reaction is a Pd^{II}-catalysed process and no re-oxidation of the palladium is required, because the HO-elimination produced palladium^{II} hydroxide species.[216] This cyclisation does not therefore involve an η^3-allylpalladium intermediate and would effectively be an aminopalladation,[217] the whole process being formally the SN2′ substitution of the allylic alcohol by the nitrogen atom.

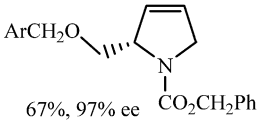


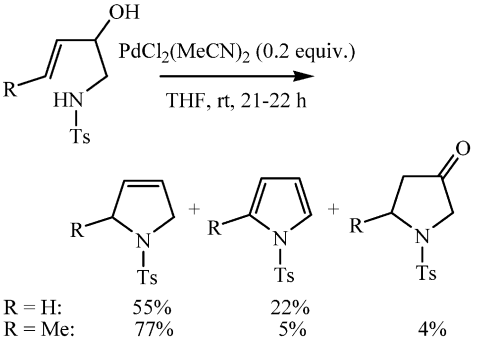
(122)

Five-membered nitrogen heterocycles, in particular dihydropyrroles, have been obtained via the 5-*endo-trig* cyclisation of 2-hydroxybut-3-enylamines (Eqs. 123 and 124).[218,219] For these cyclisations, both the allylic hydroxy group and palladium chloride were required (no reaction occured with $Pd(OAc)_2$) and, in some cases, a co-oxidant ($CuCl_2$, benzoquinone or oxygen) improved the results.[219] The formation of these compounds is rationalised as depicted in Scheme 23. Even when both the alcohol and the amine were allylic, the aminocyclisation was the only detected process (Eq. 125).[219]

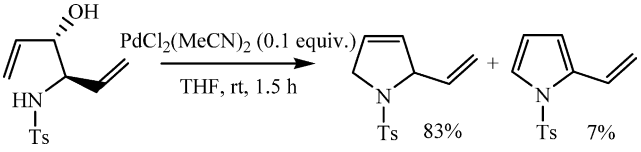


(123)



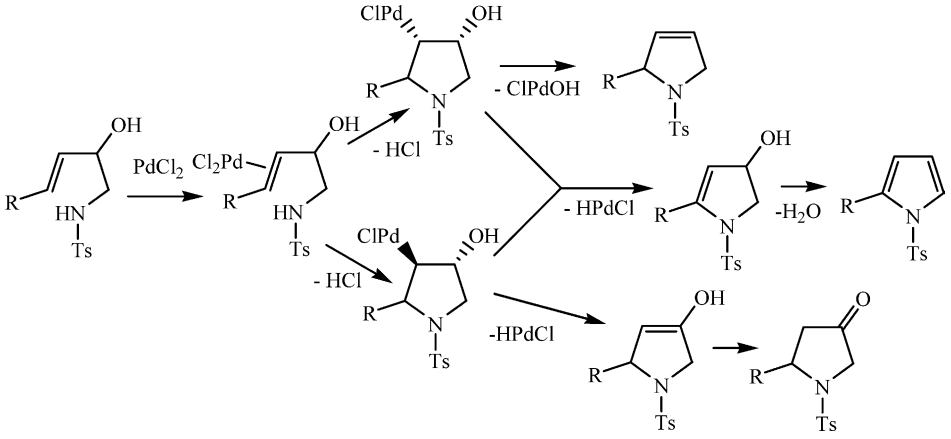


(124)

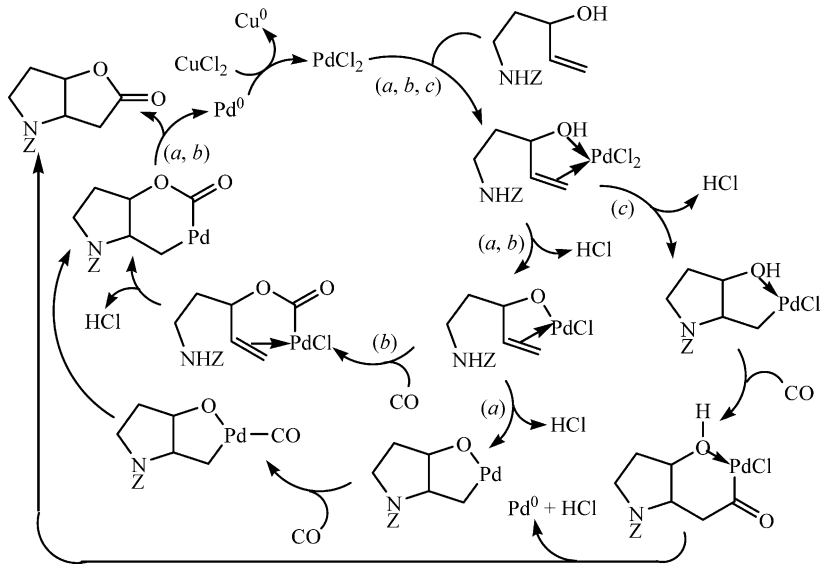


(125)

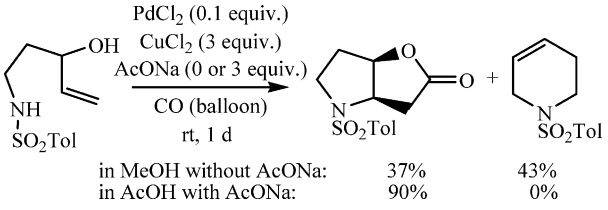
In performing the cyclisation of *N*-protected 3-hydroxy-4-pentenylamines under an atmosphere of carbon monoxide in MeOH, Tamaru et al. obtained a mixture of bicyclic pyrrolidinolactones and azacyclohex-3-enes, the formation of the former products being usually significantly improved using AcONa as additive and AcOH as solvent (Eq. 126).[220–222] This intramolecular aminocarbonylation procedure was selective, even from unsaturated aminopolyols (Eq. 127),[223,224] and was extended to *N*-protected 4-hydroxy-5-hexenylamines.[222,225]



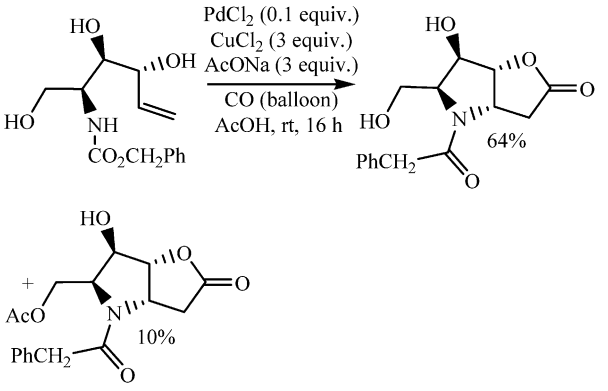
Scheme 23.



Scheme 24.



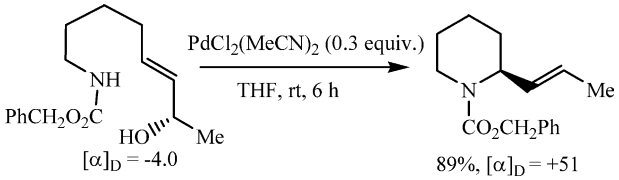
(126)



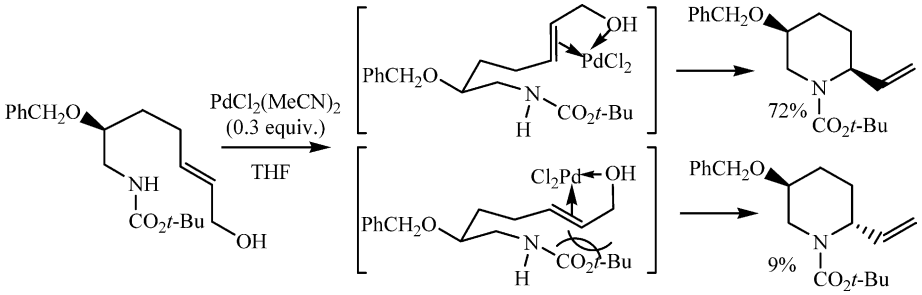
(127)

According to Jäger et al., the reaction involves an η^2-allyloxypalladium complex and two reactive pathways were proposed (Scheme 24, paths *a* and *b*), with a preference for path *a*.[226] We suggest that these aminocarbonylations could rather involve the 5-*exo*-*trig* cyclisation (path *c*) with the formation of an acylpalladium complex leading to the lactone by reaction with the hydroxy group. According to Jäger et al., copper^{II} chloride has at least a dual role: namely regeneration of the active Pd^{II} species and formation of either a copper carbonyl complex or a carbonyl complex involving both copper and palladium.[226]

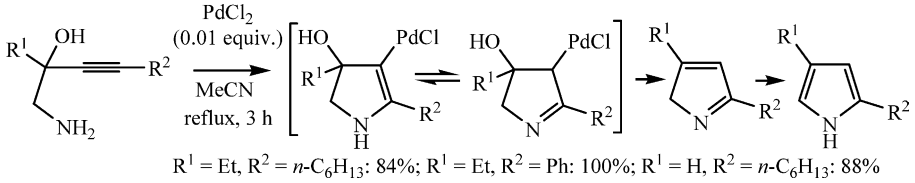
Vinylpiperidines have been produced from the 6-*exo*-*trig* cyclisation of carbamates to allylic alcohol moieties (Eqs. 128–130 and Scheme 25).[227–231] The *O*-coordination of the hydroxy group to the η^2-alkene complex leading to a chelate and the differences of repulsion with the nitrogen group at the level of the transition states have been proposed to explain the stereoselectivity of the nucleophilic addition of the nitrogen atom (Scheme. 25).[228–231] These cyclisations were the key steps of the synthesis of biologically active piperidine alkaloids such as (+)-coniine (Eq. 128),[227] SS-20846A (Eq. 129),[229] 1-deoxymannojirimycin[230] and (−)-cassine (Eq. 130).[231]



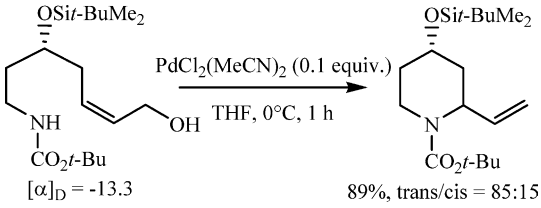
(128)



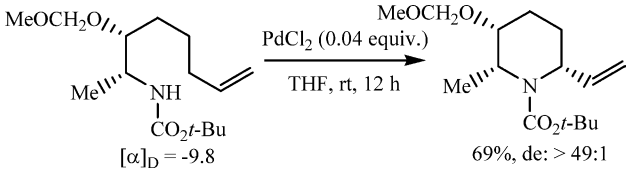
Scheme 25.



Scheme 26.



(129)

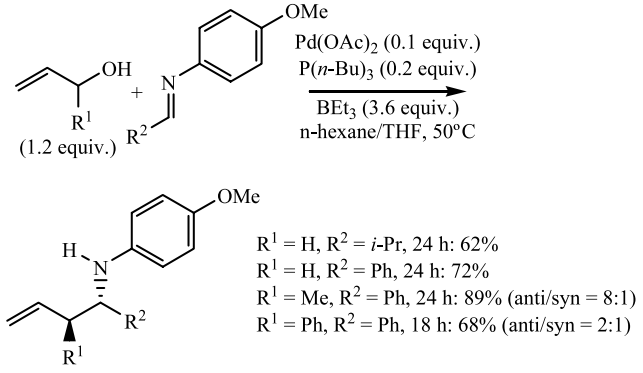


(130)

Utimoto et al. have prepared pyrroles from 1-amino-3-alkyn-2-ols and proposed the reaction course shown in Scheme 26; the catalysis with $Pd(PPh_3)_4$ was much less efficient (R^1=Et and R^2=*n*-C_6H_{13}: 17% yield) than with $PdCl_2$.[232,233]

Addendum

Tamaru et al. have reported the allylation of aldimines of aromatic and aliphatic aldehydes with allylic alcohols (Eq. 131).[234]



(131)

Hardcare et al. have examined the efficiency of the Heck arylation of 2-methylprop-2-en-ol in butyl-1-methylpyrrolidinium bis(trifluoromethylsulfonyl) amide, tetrabutylammonium bromide, *N*-methylpyrrolidinone and under solventless conditions, using a range of homogeneous and heterogeneous Pd catalysts. The ionic system has been recycled with little loss of activity.[235]

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Biographical sketch

Jacques Muzart was born in 1946, in Vienne la Ville, a small village in the Argonne area, 200 km east of Paris. He studied chemistry at the Université de Champagne-Ardenne and received his degrees (Doctorat de 3ème cycle—1972, Doctorat d'Etat—1976) for his work with Jean-Pierre Pète on photochemical rearrangements of α,β-epoxyketones and β-diketones. He was appointed at the Centre National de la Recherche Scientifique (CNRS) in 1971 as Stagiaire de Recherche and spent 15 months (1977–1978) as a postdoctoral fellow of National Science Foundation working with Elias J. Corey at Harvard University on natural product synthesis. On his return to Reims, he mainly studied the photoreactivity of η^3-allylpalladium complexes and anionic activation by supported reagents. In 1988, he was promoted to Directeur de Recherche CNRS. His research interests concentrate on transition metal-catalysis with particular emphasis on oxidations, asymmetric reactions and mechanisms. Since a few years, he is also involved in the valorisation of agricultural by-products and in the use of water and molten salts as solvents for Organic Synthesis.

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Photochemical synthesis of benzoxazolo[3,2-*b*]isoquinolin-11-one and isoquinolino[3,2-*b*][1,3]benzoxazin-11-one under basic conditions

A. Senthilvelan, D. Thirumalai and V. T. Ramakrishnan*

Department of Organic Chemistry, School of Chemical Sciences, University of Madras, Guindy Campus, Chennai 600 025, India

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Abstract—Irradiation of *N*-phenyl substituted isoquinolines in acetonitrile containing 1 M NaOH in a multilamp reactor (MLR) furnished benzoxazolo[3,2-*b*]isoquinolin-11-ones. In contrast, irradiation of the *N*-benzyl substituted isoquinoline derivative under the same conditions afforded the hydrolysed *N*-benzylbenzamide derivative. The isoquinolinobenzoxazine was obtained by irradiating the *N*-benzyl substituted isoquinoline derivative at higher basic conditions. The required isoquinolines were synthesized under solvent-free, solid supported microwave conditions.

1. Introduction

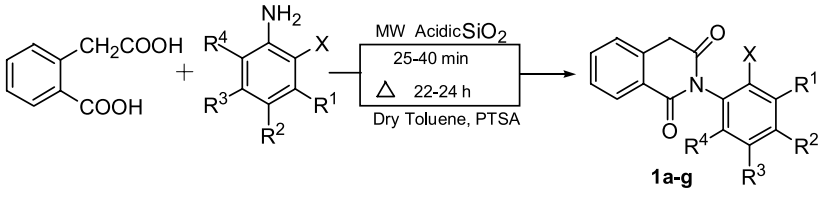
Isoquinoline fused alkaloids play an important role in the field of medicine as antihypertensive agents and antidepressant agents.[1,2] Tetrahydroisoquinolines are the building blocks for the syntheses of various isoquinolinoalkaloids.[3,4] Oxazoles and oxazines are known to exhibit a broad spectrum of biological activities.[5,6] Recently, the synthesis of benzoxazoles[7] and benzoxazines[8] has been reported. Microwave-assisted organic synthesis is a new and growing area in synthetic organic chemistry. The combination of supported reagents and microwave irradiation can be used to carry out a wide range of reactions in short times with high conversions, without the need for solvents.[9]

In continuation of our interest on the photochemistry of heterocycles, we have reported the photochemical synthesis of benzothiazoles,[10,11] triazolobenzothiazoles,[12] and triazolobenzothiazines.[13,14] In a preliminary communication,[15] we have reported the first photochemical synthesis of isoquinoline-fused benzoxazole and benzoxazine derivatives. In this paper, we wish to report the systematic study on the thermal and microwave assisted synthesis of tetrahydroisoquinolines and their photolysis under base-mediated conditions.

2. Results and discussion

2.1. Synthesis of isoquinolines

The isoquinolines were synthesized by a direct one-step process under thermal and solvent-free, solid supported microwave conditions. In the thermal conditions, refluxing a mixture of homophthalic acid (1 equiv), substituted aniline (1 equiv) and *p*-toluenesulfonic acid (catalytic amount) in dry toluene using a Dean–Stark apparatus for 22–24 h furnished the corresponding tetrahydroisoquinoline-1,3-dione **1a–g** (Scheme 1) in good yield in one-step. In the



Scheme 1.

Keywords: Isoquinolines; Cyclization; Benzoxazoles; Benzoxazine.
* Corresponding author. Tel.: +91 44 2235 1269x213; fax: +91 44 2235 2494; e-mail: vtrk28@yahoo.com

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Table 1. Synthesis of tetrahyroisoquinoline-1,3-dione **1a–g** under thermal and microwave condition

1	X	R^1	R^2	R^3	R^4	Microwave condition		Thermal condition	
						Time (min)	Yield (%)	Time (h)	Yield (%)
1a	Cl	H	H	H	H	25	67	22	70
1b	Cl	Cl	H	H	H	25	73	24	68
1c	Cl	H	Cl	H	H	30	58	23	62
1d	Cl	H	H	Cl	H	30	62	24	66
1e	Cl	H	H	H	Cl	40	65	24	70
1f	Br	H	CH_3	H	H	30	78	24	75
1g	Br	H	H	H	H	35	69	24	72

microwave conditions, the synthetic procedure generally involved impregnating the solid support with homophthalic acid with the substituted anilines in methylene chloride solution, evaporating the solvent, and heating the solid residue in a microwave oven. Preliminary optimization of reaction conditions was carried out using solid supports like neutral alumina, anhydrous sodium sulfate, anhydrous magnesium sulfate and acidic silica gel. Among different supports tested, the expected isoquinolines **1a–g** were formed in higher yields when acidic silica gel was used (Scheme 1). Optimal conditions for the synthesis were found to be 25–40 min reaction time, with a cut-off of the MW irradiation after every 5 min (to monitor the progress of the reaction), using microwave irradiation power of 800 W. No reaction was observed in the absence of MW irradiation or when the solid support was omitted from the reaction mixture.

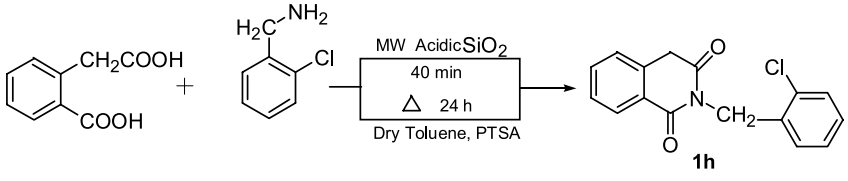
Under classical thermal conditions using high boiling solvent such as toluene in the presence of *p*-toluenesulfonic acid (PTSA), a much longer reaction time (22–24 h) was required. In contrast, with microwave irradiation, the time did not exceed 40 min for completion of the reaction. The comparative data is shown in Table 1. Likewise, the reaction of homophthalic acid with 2-chlorobenzylamine in the presence of *p*-toluenesulfonic acid required 24 h under thermal condition, but only 40 min for the solid-supported MW irradiation condition, to afford the *N*-(2-chlorobenzyl)-tetrahydroisoquinoline-1,3-dione **1h** (Scheme 2).

The products **1a–h** were characterized by spectral and analytical data. The IR spectra of compounds **1a–h** showed the C_3-carbonyl group around 1700 cm^{-1} and the C_1-carbonyl group around 1600 cm^{-1}. In the ^1H NMR spectra of compounds **1b** and **1g**, geminal coupling was observed for C_4-CH_2 protons with $J=22.5$ Hz around δ 4, while for compounds **1a**,**c**,**d**,**f** the J value could not be determined, because the splitting pattern was not resolved. In the case of compound **1e**, due to the symmetrical substituents in the *N*-aryl ring, no geminal coupling of C_4-CH_2 protons was observed. The C_8-ArH of compounds **1a–h** showed doublet around δ 8 due to the deshielding effect of the C_1-carbonyl group. The structure of the compounds **1b**,**f**,**h** were further confirmed by XRD analysis.[16]

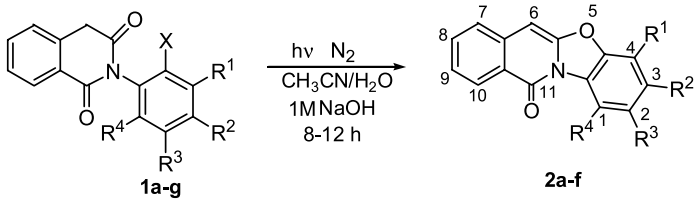
2.2. Irradiation studies

An acetonitrile solution (150 mL) of the isoquinoline **1a** (0.3 g, 1.1 mmol), containing 30 mL of aqueous 1 M NaOH, was flushed with nitrogen for 1 h and irradiated at 254 nm in an Applied Photophysics multilamp reactor (MLR) for 12 h. Usual work-up and chromatographic purification furnished the benzoxazolo[3,2-*b*]isoquinolin-11-one **2a** in 41% yield (Scheme 3). Similarly, irradiation of compounds **1b–f**, in acetonitrile containing 1 M NaOH in a multilamp reactor for 8–12 h, furnished the corresponding substituted benzoxazolo[3,2-*b*]isoquinolin-11-ones **2b–f** (Table 2). Photolysis of the bromo analogue **1g** also afforded **2a**, which was confirmed by mp, mixture mp and superimposable IR spectrum with that obtained under the same conditions from **1a**.

The photosubstitution reaction described here has to involve replacement of the halogen atom present in the *N*-phenyl moiety of the isoquinoline-1,3-diones **1a–g** by the carbonyl oxygen (C_3-CO) intramolecularly. A dark experiment



Scheme 2.



Scheme 3.

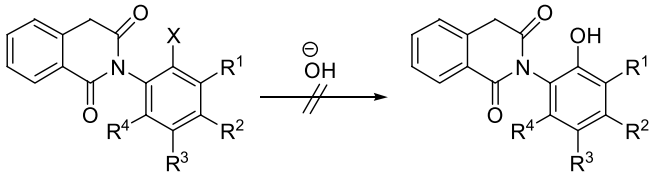
Table 2. Photolysis of isoquinoline **1a–g** to benzoxazolo isoquinoline **2a–f**

1	X	R^1	R^2	R^3	R^4	Irradiation time (h)	2	Yield of **2** (%)
1a	Cl	H	H	H	H	12	**2a**	41
1b	Cl	Cl	H	H	H	7	**2b**	43
1c	Cl	H	Cl	H	H	8	**2c**	48
1d	Cl	H	H	Cl	H	9	**2d**	46
1e	Cl	H	H	H	Cl	10	**2e**	40
1f	Br	H	CH_3	H	H	7	**2f**	52
1g	Br	H	H	H	H	8	**2a**	50

(without irradiation) of **1a** for 30 h did not produce any product. Thus the formation of benzoxazolo[3,2-*b*]isoquinolin-11-one is not due to the thermal reaction, but due to the photoinduced substitution reaction.

In presence of base such as NaOH, the UV–Vis absorption (λ_{max}) behavior of the isoquinoline **1a** in acetonitrile was changed from 247 to 314 nm. The species at 314 nm is believed to be the enolate. Thus anionic species are probably formed in solution, which induces the photosubstitution. One possible explanation is that the enolate oxygen intramolecularly displaces the halogen of the haloarene in the singlet excited state (S_N2Ar^*).[17] Another possibility is that a radical anion intramolecularly substitutes the halogen of the haloarene ($S_N(ET)Ar^*$).[17]

The photosubstitution reactivity depends on the leaving ability of the halide ion. Bromoanalogue **1g** is more reactive, which is reflected in the formation of the photosubstituted product **2a** in higher yield and in a shorter reaction time compared to the chloro analogue **1a** (Table 2). Thus the rate-determining step of the reaction is the leaving halide anion. Moreover, if the S_N2Ar^* mechanism is operative, a phenolic-type product could be formed from intermolecular substitution of the halide ion with the hydroxyl group (Scheme 4). Such a product was not detected in the reaction conditions. From these results, it is viewed that the photosubstitution reaction is more likely occurring by the intramolecular $S_N(ET)Ar^*$ mechanism and not the S_N2Ar^*mechanism.

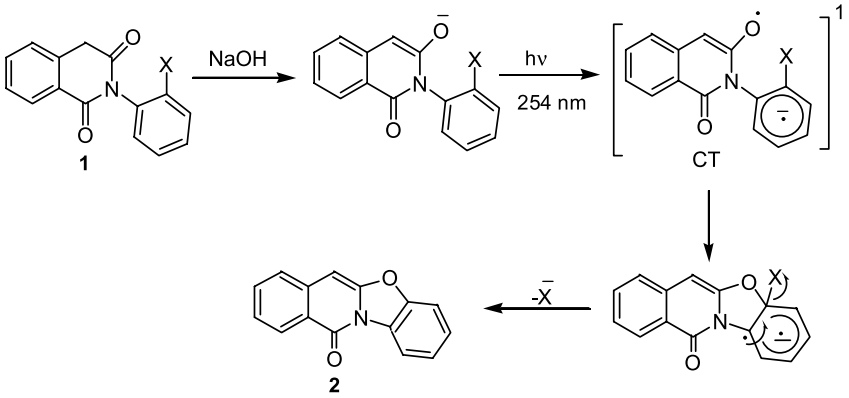


Scheme 4.

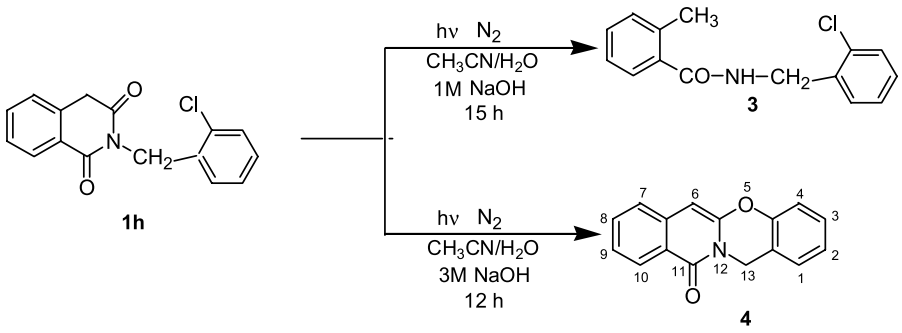
The probable mechanistic pathway is described in Scheme 5. The light absorption of enolate anion populates the intramolecular charge transfer (CT) singlet excited state, which produces a cyclohexadienyl anion radical by intramolecular addition of the oxygen radical of the enolate to the anionic halophenyl moiety in the charge transfer excited state, which in turn yields the benzoxazolo[3,2-*b*]isoquinoline **2** by the ejection of the halide ion.

A similar intramolecular electron-transfer mechanism has been proposed for 2-(pyridinyl)benzoxazoles.[18] The intramolecular electron transfer mechanism for the formation of benzothiazoles from the photoreaction of *o*-halothioacetanilide, by observing the $Cl_2^{\bullet-}$ anion radical at $\lambda_{max} \sim 345$ nm in laser flash and steady state experiments has been proposed for the first time from our laboratory.[12]

The structure of photoproducts **2a–f** were consistent with the spectroscopic data. The IR spectra showed the disappearance of the C_3-CO group of isoquinoline **1a–g** around 1700 cm^{-1}. It showed the C_{11}-CO group around 1650 cm^{-1}. The ^1H NMR spectra showed the C_6-CH proton of **2a–f** around δ 6.5, which indicates the disappearance of the C_4–CH_2 proton of isoquinolines **1a–g**. The ^{13}C NMR spectra also confirmed the presence of C_6-CH carbon and C_{11}-CO carbon, which appear around δ 82 and δ 159, respectively. Furthermore, the structure of compound **2c** was confirmed by XRD.[19]



Scheme 5.



Scheme 6.

2.3. Irradiation of the isoquinoline 1h

The irradiation of isoquinoline-1,3-dione **1h** (1.0 mmol) for 15 h in acetonitrile containing 1 M NaOH (30 mL) was carried out (after flushing with nitrogen for 1 h) in a multilamp reactor (254 nm). After completion of the reaction, usual work-up and chromatographic separation afforded the hydrolysed *N*-(2-chlorobenzyl)-2-methylbenzamide **3** (Scheme 6) instead of the expected isoquinolinobenzoxazine.

The hydrolysis product **3** was confirmed by spectroscopic and analytical data. The IR spectrum of compound **3** showed –NH peak at 3296 cm^{-1} and carbonyl peak at 1641 cm^{-1}. The ^1H NMR spectrum showed the $-CH_3$ protons at δ 2.41, $-CH_2$ protons at δ 4.68 as a doublet with coupling constant $J=6$ Hz and –NH proton at δ 6.25 as a broad singlet. The ^{13}C NMR of the compound **3** indicated the presence of $-CH_3$ carbon at δ 19.7, $-CH_2$ carbon at δ 41.8 and CO carbon at δ 169.8. Furthermore, the compound **3** was confirmed by mp, mixture mp and superimposable IR spectra with the authentic sample prepared from 2-methyl benzoylchloride and 2-chlorobenzylamine in dry benzene.

The formation of hydrolysis product is probably due to ineffective population of the enolate of **1h** in 1 M NaOH and the molecular flexibility of the *N*-benzyl substituent, which causes the base mediated hydrolysis followed by photodecarboxylation of **1h** to **3**. Light induced decarboxylation of (*o*-acylphenyl)acetic acids has been reported.[20]

In order to effect the photosubstitution reaction, we carried out the photolysis of **1h** under higher basic conditions. Hence, irradiation of **1h** (1.0 mmol) in acetonitrile containing 3 M NaOH (30 mL) was carried out for 12 h (after flushing with nitrogen for 1 h) in a multilamp reactor. The expected product isoquinolino[3,2-*b*][1,3]benzoxazin-11-one **4** was isolated.

The compound **4** was confirmed by spectroscopic and analytical data. The IR spectrum of **4** shows the disappearance of C_3-CO group of **1h** and shows the C_{11}-CO group at 1689 cm^{-1}. The ^1H NMR spectrum of **4** showed the C_{13}-CH_2 proton at δ 5.16, the C_6-CH proton at δ 6.21 and the C_4-aromatic proton at δ 8.33 as a doublet with coupling constant $J=7.8$ Hz. The remaining seven aromatic protons appeared as a multiplet at δ 7.12–7.60. The ^{13}C NMR also indicated the C_{13}-CH_2 carbon at δ 40.7, the C_6-CH carbon at δ 87.8 and the C_{11}-CO carbon at δ 161.9.

3. Conclusions

The tetrahydroisoquinoline-1,3-diones **1a–h** were synthesized in comparable yield, under solid supported solvent-free microwave conditions in shorter reaction time (<1 h) compared to the classical thermal conditions. Irradiation of tetrahydroisoquinoline **1a–g** under base mediated conditions (CH_3CN/1 M NaOH) in a multilamp reactor (MLR) afforded the respective benzoxazolo[3,2-*b*]isoquinolin-11-one **2a–f** in good yield. Photolysis of isoquinoline **1h** in CH_3CN/1 M NaOH using a multilamp reactor furnished the hydrolysed *N*-(2-chlorobenzyl)-2-methylbenzamide **3**, whereas irradiation at higher basic conditions such as acetonitile containing 3 M NaOH afforded the expected product isoquinolino[3,2-*b*][1,3]-benzoxazin-11-one **4**.

4. Experimental

4.1. General

All the melting points are uncorrected. UV spectra were recorded with Shimadzu 1601 spectrophotometer. IR spectra were recorded on Shimadzu FTIR-8300 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded with Brucker-DPX 200 (200 MHz) and Jeol-GSX 400 (400 MHz) instruments with TMS as internal standard (chemical shift in δ ppm). The mass spectra were recorded with Jeol-JMS-DX 303 HF (EI, 70 eV) and GCMS QP 5000 Shimadzu instruments. Chromatographic separations were done using silica gel (ACME sample). Thin layer chromatography (TLC) was performed using glass plates coated with silica gel (ACME sample) of 0.25 mm thickness. Spots were visualized using iodine vapour. The photochemical reactions were carried out in quartz vessel of different capacity in Applied Photophysics multilamp reactor (254 nm, 12 lamps). Microwave reactions were carried out in Kenstar-India microwave oven (800 W).

4.2. General procedure for the synthesis of substituted tetrahydroisoquinoline-1,3-diones 1a–h

The tetrahydroisoquinolines were synthesized from the corresponding homophthalic acid and substituted anilines and benzylamine by a direct one-step procedure under thermal and solvent-free solid supported microwave conditions.

(i) *Thermal conditions*. A mixture of homophthalic acid (1 equiv), substituted amine (1 equiv) and *p*-toluenesulfonic acid (catalytic amount) was refluxed in dry toluene using a Dean–Stark apparatus for 22–24 h. After completion of the reaction, monitored by TLC, the reaction mixture was cooled to room temperature, extracted with ethyl acetate and the organic layer washed with H_2O, dil. HCl and dil. $NaHCO_3$. The ethyl acetate layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The solid obtained was filtered and recrystallized from ethyl acetate–hexane mixture, to furnish the corresponding tetrahydroisoquinoline-1,3-dione **1a**–**h** in good yield.

(ii) *Microwave conditions*. A thoroughly ground mixture of homophthalic acid (1 equiv) and acidic silica gel (3–5 g) was mixed with a methylene chloride solution of substituted amine (1 equiv). The solvent was removed under reduced pressure; the solid residue was placed in a (Kenstar-India) microwave oven (800 W), irradiated for 5 min, cooled, and again irradiated for 5 min. The procedure was continued for a total MW irradiation time of 25–40 min. After completion of the reaction, checked by TLC, it was cooled to room temperature. The mixture was extracted with ethyl acetate and filtered. The filtrate was washed with water, dil. HCl, and dil. $NaHCO_3$, dried over anhydrous Na_2SO_4 and concentrated. The solid obtained was filtered and recrystallized from ethyl acetate–hexane mixture. The isoquinolines thus formed were compared by mp, mixture mp and superimposable IR spectra with **1a**–**h** obtained under thermal conditions.

4.2.1. *N*-(2-Chlorophenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione 1a. A mixture of homophthalic acid (1 g, 5.0 mmol), *o*-chloroaniline (0.7 g, 5.0 mmol) and *p*-toluenesulfonic acid (catalytic amount) in toluene (50 mL) was refluxed using a Dean–Stark apparatus for 22 h. After completion of the reaction, usual work-up as mentioned above furnished **1a**. Yield: 1.05 g (70%); mp 110–112 °C; UV 246 nm (CH_3CN); IR (KBr): 1720 (C_3-CO), 1679 (C_1-CO) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 4.28 (bs, 2H, C_4-CH_2), 7.23–7.67 (m, 7H, Ar–H), 8.24 (d, $J=7.7$ Hz, 1H, C_8-H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 36.8, 125.1, 127.5, 127.8, 127.9, 129.5, 130.2, 130.4, 132.7, 133.2, 134.1, 134.2, 164.3 (C_1-CO), 169.1 (C_3-CO). MS: *m*/*z* (%): (271 (M^+), 273-trace), 236 (100), 235 (3), 208 (38), 180 (5), 179 (4), 118 (12), 117 (6), 104 (6), 90 (37), 89 (32), 63 (12). Anal. Calcd for $C_{15}H_{10}NO_2Cl$ (271.698): C, 66.30; H, 3.70; N, 5.15; Found: C, 66.52; H, 3.51; N, 5.40.

A mixture of homophthalic acid (0.3 g, 1.6 mmol), *o*-chloroaniline (0.21 g, 1.6 mmol) and acidic silica gel (3 g) was irradiated in the microwave oven for 25 min. After completion of the reaction, usual work up as mentioned above afforded **1a** (yield=67%). Refluxing a mixture of homophthalic anhydride (1 g, 6.2 mmol), *o*-chloroaniline (0.78 g, 6.2 mmol) and *p*-toluenesulfonic acid in dry toluene (100 mL) using a Dean–Stark apparatus for 24 h, followed by usual work up, afforded **1a** (yield=0.33 g, 20%).

4.2.2. *N*-(2,3-Dichlorophenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione 1b. Following the general procedure, a mixture of homophthalic acid (2.5 g, 13.8 mmol), 2,3-dichloroaniline (2.25 g, 13.8 mmol) and *p*-toluenesulfonic acid in dry toluene (120 mL) was refluxed for 24 h. After completion of the reaction, usual work-up furnished **1b**. Yield: 2.87 g (68%); mp 198–200 °C; UV: 242 nm (CH_3CN); IR (KBr): 1728 (C_3-CO), 1679 (C_1-CO) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.20 (d, $J=22.5$ Hz, 1H, C_4-H_a), 4.28 (d, $J=22.5$ Hz, 1H, C_4-H_b), 7.18–7.68 (m, 6H, Ar–H), 8.24 (d, $J=7.8$ Hz, 1H, C_8-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 36.8, 124.9, 127.4, 127.7, 127.9, 128.6, 129.5, 131.0, 131.7, 134.1, 134.1, 134.3, 134.8, 164.1 (C_1-CO), 168.9 (C_3-CO). MS: *m*/*z* (%): (305 (M^+), 307-trace), 270 (100) [272 (33)], 269 (2), 242 (46) [244 (15)], 214 [216], 213 [215], 152 [154], 118 (15), 117 (4), 104 (2), 90 (58), 89 (58), 63 (16).The structure of the compound was further confirmed by XRD.[16]

A mixture of homophthalic acid (0.3 g, 1.6 mmol), 2,3-dichloroaniline (0.27 g, 1.6 mmol) and acidic silica gel (3 g) was heated in the microwave oven for 25 min. Usual work-up afforded **1b** (yield=73%).

4.2.3. *N*-(2,4-Dichlorophenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione 1c. A mixture of homophthalic acid (4 g, 22.2 mmol), 2,4-dichloroaniline (3.6 g, 22.2 mmol) and *p*-toluenesulfonic acid in dry toluene (150 mL) was refluxed for 23 h; the usual work-up afforded **1c**. Yield: 4.21 g (62%); mp 160–162 °C; UV: 240 nm (CH_3CN); IR (KBr): 1732 (C_3-CO), 1678 (C_1-CO) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 4.20 (bs, 2H, C_4-CH_2), 7.16−7.68 (m, 6H, Ar–H), 8.22 (d, $J=7.8$ Hz, 1H, C_8-H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 36.8, 124.9, 127.5, 128.0, 128.1, 129.5, 130.2, 131.3, 131.9, 133.6, 134.2, 134.3, 135.5, 164.1 (C_1-CO), 169.0 (C_3-CO). MS: *m*/*z* (%): (305 (M^+), 307-trace), 270 (100) [272 (33)], 269 (2), 242 (46) [244 (14)], 214 [216], 213 [215], 152 [154], 118 (14), 117 (5), 104 (4), 90 (60), 89 (60), 63 (20). Anal. Calcd for $C_{15}H_9NO_2Cl_2$ (306.143): C, 58.84; H, 2.96; N, 4.57. Found: C, 58.62; H, 3.11; N, 4.72.

Microwave irradiation of a mixture of homophthalic acid (0.4 g, 2.2 mmol), 2,4-dichloroaniline (0.36 g, 2.2 mmol) and acidic silica gel (4 g) for 30 min furnished **1c** (yield=58%), after usual work-up.

4.2.4. *N*-(2,5-Dichlorophenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione 1d. Refluxing a mixture of homophthalic acid (4 g, 22.2 mmol), 2,5-dichloroaniline (3.6 g, 22.2 mmol) and *p*-toluenesulfonic acid in dry toluene (150 mL) for 24 h, followed by usual work-up furnished **1d**. Yield: 4.48 g (66%); mp 158–160 °C; UV: 240 nm (CH_3CN); IR (KBr): 1728 (C_3-CO), 1679 (C_1-CO) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 4.23 (bs, 2H, C_4-CH_2), 7.27–7.70 (m, 6H, Ar–H), 8.23 (dd, $J=7.8$, 1.1 Hz, 1H, C_8-H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 37.2, 125.3, 127.9, 128.5, 130.0, 130.5, 130.8, 131.1, 131.4, 131.7, 133.6, 134.6, 134.8, 164.5 (C_1-CO), 169.3 (C_3-CO). MS: *m*/*z* (%): (305 (M^+), 307-trace), 270 (100) [272 (33)], 269 (2), 242 (32) [244 (10)], 214 [216], 213 [215], 152 [154], 118 (9), 117 (6), 104 (2), 90 (30), 89 (28), 63 (8). Anal. Calcd for $C_{15}H_9NO_2Cl_2$ (306.143): C, 58.84; H, 2.96; N, 4.57. Found: C, 58.63; H, 3.13; N, 4.68.

A mixture of homophthalic acid (0.3 g, 1.6 mmol), 2,5-dichloroaniline (0.27 g, 1.6 mmol) and acidic silica gel (3 g)

was heated in the microwave oven for 30 min. After completion of the reaction, usual work-up afforded **1d** (yield = 62%).

4.2.5. *N*-(2,6-Dichlorophenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione 1e. A toluene (150 mL) solution of homophthalic acid (4 g, 22.2 mmol), 2,6-dichloro aniline (3.6 g, 22.2 mmol) and *p*-toluenesulfonic acid was refluxed for 24 h; usual work-up afforded **1e**. Yield: 4.75 g (70%); mp 170–172 °C; UV: 244 nm (CH_3CN); IR (KBr): 1720 (C_3-CO), 1674 (C_1-CO) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 4.24 (s, 2H, C_4-CH_2), 7.27–7.68 (m, 6H, Ar–H), 8.26 (d, J = 7.8 Hz, 1H, C_8-H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 37.2, 125.3, 128.0, 128.4, 129.0, 130.0, 130.6, 131.0, 134.8, 135.0, 134.8, 164.5 (C_1-CO), 168.8 (C_3-CO). MS: *m/z* (%): (305 (M^+), 307-trace), 270 (100) [272 (33)], 242 (38) 213 [215], 152 [154], 118 (25), 117 (4), 104 (2), 90 (68), 63 (30). Anal. Calcd for $C_{15}H_9NO_2Cl_2$ (306.14): C, 58.84; H, 2.96; N, 4.57. Found: C, 58.72; H, 3.17; N, 4.77.

A mixture of homophthalic acid (0.4 g, 2.2 mmol), 2,3-dichloroaniline (0.36 g, 2.2 mmol) and acidic silica gel (4 g) was heated in the microwave oven for 40 min; usual work-up afforded **1e** (yield = 65%).

4.2.6. *N*-(2-Bromo-4-methylphenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione 1f. Following the general procedure, a mixture of homophthalic acid (4 g, 22.2 mmol), 2-bromo-4-methylaniline (4.13 g, 22.2 mmol) and *p*-toluenesulfonic acid in dry toluene (150 mL) was refluxed for 24 h. After completion of the reaction, usual work-up furnished **1f**. Yield: 5.47 g (75%); mp 162–164 °C; UV: 245 nm (CH_3CN); IR (KBr): 1722 (C_3-CO), 1679 (C_1-CO) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.36 (bs, 3H, CH_3), 4.18 (s, 2H, C_4-CH_2), 7.09–7.63 (m,6H, Ar–H), 8.21 (d, J = 7.7 Hz, 1H, C_8-H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.5, 37.4, 123.0, 125.7, 128.0, 128.3, 129.8, 129.9, 130.4, 132.6, 134.3, 134.6, 134.8, 141.4, 164.8 (C_1-CO), 169.7 (C_3-CO). MS: *m/z* (%): (329 (M^+), 331-trace), 250 (100), 249 (2), 222 (42), 194 (2), 193 (2), 132 (10), 118 (8), 117 (3), 104 (5), 90 (40), 89 (39), 63 (12). Anal. Calcd for $C_{16}H_{12}NO_2Br$ (330.176): C, 58.20; H, 3.66; N, 4.24. Found: C, 58.46; H, 3.57; N, 4.42. Further the structure was confirmed by XRD.[16]

Heating a mixture of homophthalic acid (0.5 g, 2.7 mmol), 2-bromo-4-methylaniline (0.52 g, 2.7 mmol) and acidic silica gel (5 g) in microwave oven for 30 min, followed by usual work-up furnished **1f** (yield = 78%).

4.2.7. *N*-(2-Bromophenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione 1g. A mixture of homophthalic acid (3 g, 16.6 mmol), 2-bromoaniline (2.86 g, 16.6 mmol) and *p*-toluenesulfonic acid in dry toluene (120 mL) was refluxed for 24 h. After completion of the reaction, usual work-up afforded **1g**. Yield: 3.76 g (72%); mp 126–128 °C; UV: 242 nm (CH_3CN); IR (KBr): 1712 (C_3-CO), 1676 (C_1-CO) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.19 (d, J = 22.5 Hz, 1H, C_4-H_a), 4.28 (d, J = 22.5 Hz, 1H, C_4-H_b), 7.25 − 7.73 (m, 7H, Ar–H), 8.24 (d, J = 7.3 Hz,1H,C_8-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 36.8, 122.8, 125.1, 127.4, 127.9, 128.4, 129.5, 130.3, 130.4, 133.3, 134.1, 134.2, 134.8, 164.2 (C_1-CO), 169.1 (C_3-CO). MS: *m/z* (%): (315 (M^+), 317-trace), 236 (100), 235 (2), 208 (48), 180 (6), 179 (4), 118 (12), 117 (2), 104 (8), 90 (38), 89 (33), 63 (10). Anal. Calcd for $C_{15}H_{10}NO_2Br$ (316.15): C, 56.98; H, 3.18; N, 4.43. Found: C, 56.77; H, 3.29; N, 4.58.

Microwave irradiation of a mixture of homophthalic acid (0.4 g, 2.2 mmol) and 2-bromoaniline (0.38 g, 2.2 mmol) in acidic silica gel (4 g) for 35 min, furnished **1g** (yield = 69%).

4.2.8. *N*-(2-Chlorobenzyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione 1h. Following the general procedure, a mixture of homophthalic acid (3 g, 16.6 mmol), 2-chlorobenzylamine (2.35 g, 16.6 mmol) and *p*-toluenesulfonic acid was refluxed in dry toluene (120 mL) for 24 h. After completion of the reaction, usual work- up furnished **1h**. Yield: 3.36 g (71%); mp 122–124 °C; UV: 244 nm (CH_3CN); IR (KBr): 1718 (C_3-CO), 1670 (C_1-CO) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 4.18 (s, 2H, C_4-CH_2), 5.28 (s, 2H, N–CH_2), 7.02–7.64 (m, 7H, Ar–H), 8.20 (d, J = 7.7 Hz, 1H, C_8-H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 36.5, 41.3, 125.1, 126.8, 127.2, 127.3, 127.9, 128.3, 129.4, 129.6, 133.0, 133.9, 134.0, 134.1, 164.7 (C_1-CO), 169.8 (C_3-CO). MS: *m/z* (%): (285 (M^+), 287-trace), 250 (100), 249 (1), 222 (13), 194 (2), 166 (4), 132 (2), 125 (6), 118 (12), 104 (3), 90 (20), 89 (22), 63 (2). Anal. Calcd for $C_{16}H_{12}NO_2Cl$ (285.725): C, 67.25; H, 4.23; N, 4.90. Found: C, 67.17; H, 4.42; N, 5.12. Further the compound was confirmed by XRD.[16]

Heating a mixture of homophthalic acid (0.5 g, 2.7 mmol), 2-chlorobenzylamine (0.38 g, 2.7 mmol) and acidic silica gel (5 g) in microwave oven for 40 min, followed by usual work-up furnished **1h** (yield = 65%).

4.3. Irradiation of the tetrahydroisoquinolines 1a–g

4.3.1. Benzoxazolo[3,2-*b*]isoquinolin-11-one 2a. An acetonitrile solution (150 mL) of *N*-(2-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione **1a** (0.3 g, 1.1 mmol) containing 30 mL of aqueous 1 M NaOH was flushed with nitrogen for 1 h and irradiated at 254 nm in an Applied Photophysics multilamp reactor for 12 h. The reaction was monitored by TLC until the disappearance of the starting material. After completion of the reaction, the solvent was evaporated under reduced pressure from the two-phase mixture and it was extracted with ethyl acetate. The ethyl acetate layer was separated, the aqueous layer was neutralized with dil. HCl, and then was extracted with ethyl acetate. The ethyl acetate portions were combined together, dried over anhydrous Na_2SO_4, and concentrated. The residue was chromatographed over a column of silica gel; elution with ethyl acetate-petroleum ether (15:85) furnished the respective benzoxazolo[3.2-*b*]isoquinolin-11-one **2a**. It was recrystallized from ethyl acetate-hexane mixture. Yield: 0.106 g (41%); mp 200–202 °C (lit.[21] mp 204–206 °C); UV: 234 nm (CH_3OH); IR (KBr): 1685, 1625, 1606, 1473 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 6.45 (s, 1H, C_6-CH), 7.19–7.51 (m, 4H, ArH), 7.51–7.85 (m, 2H, ArH), 8.29–8.75 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 81.9 (C_6-CH), 109.9, 116.4, 119.6, 121.5, 124.2, 124.3, 125.9, 126.2, 127.8, 132.8, 137.7, 147.2, 149.9, 159.3 (C_{11}-CO). MS: *m/z* (%): 235 (M^+, 100), 234

(12), 207 (6), 206 (5), 179 (2), 178 (6), 177 (2), 151 (5), 125 (2), 117.5 (M^{++}), 115 (2), 101 (2), 89 (12).

Irradiation of *N*-(2-bromophenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione **1g** (0.3 g, 3.1 mmol) in acetonitrile (150 mL) containing 1 M NaOH (30 mL) for 8 h, using multilamp reactor (MLR), followed by usual work-up and chromatographic separation, afforded **2a** (yield = 50%), which was confirmed by mp, mixture mp and superimposable IR with that obtained under the same conditions from **1a**.

4.3.2. 4-Chlorobenzoxazolo[3,2-*b*]isoquinolin-11-one 2b. Irradiation of *N*-(2,3-dichlorophenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione **1b** (0.3 g, 1.0 mmol) in acetonitrile (150 mL) containing 1 M NaOH (30 mL) for 7 h, using multilamp reactor, followed by usual work-up as mentioned above and chromatographic separation, furnished **2b**.Yield: 0.113 g (43%); mp 188–190 °C; UV: 242 nm (CH_3OH); IR (KBr): 1678, 1642, 1604, 1468 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.54 (s, 1H, C_6-CH), 7.26–7.88 (m, 5H, ArH), 8.42–8.50 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 82.6 (C_6-CH), 114.7, 115.4, 122.2, 124.9, 125.1, 126.5, 128.5, 129.1, 130.1, 133.2, 137.4, 146.1, 149.5, 159.2 (C_{11}-CO). MS: *m/z* (%): 269 (M^+, 100), 271 (M+2, 30), 241 (15) [243 (6)], 234 (9), 213 (5) [215 (2)], 206 (22), 178 (30), 177 (17), 151 (8), 134.5 (M^{++}, 5), 125 (3), 115 (9), 101 (5), 89 (15). Anal. Calcd for $C_{15}H_8NO_2Cl$ (269.68): C, 66.80; H, 2.98; N, 5.19. Found: C, 66.67; H, 3.21; N, 5.37.

4.3.3. 3-Chlorobenzoxazolo [3,2-*b*] isoquinolin-11-one 2c. The compound **2c** was obtained on irradiation of *N*-(2,4-dichlorophenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione **1c** (0.3 g, 1.0 mmol) in acetonitrile (150 mL) containing 1 M NaOH (30 mL) for 8 h, using multilamp reactor. Yield: 0.126 g (48%); mp 205–207 °C; UV: 243 nm (CH_3OH); IR (KBr): 1683, 1643, 1606, 1475 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.47 (s, 1H, C_6-CH), 7.32–7.69 (m, 5H, ArH), 8.44 (d, J = 8.3 Hz, 1H, C_1-ArH), 8.48 (d, J = 8.3 Hz, 1H, C_2-ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 82.3 (C_6-CH), 110.8, 116.7, 121.9, 124.4, 124.8, 126.1, 126.8, 127.8, 131.9, 133.0, 137.8, 147.8, 150.0, 159.5 (C_{11}-CO). MS: *m/z* (%): 269 (M^+, 100), 271 (M+2, 36), 241 (8) [243 (3)], 234 (9), 213 (6) [215 (2)], 206 (22), 178 (16), 177 (8), 151 (8), 134.5 (M^{++}, 8), 125 (2), 115 (3), 101 (8), 89 (10). The structure of the compound was further confirmed by XRD.[19]

4.3.4. 2-Chlorobenzoxazolo [3,2-*b*] isoquinolin-11-one 2d. Irradiation of an acetonitrile (150 mL) solution of *N*-(2,5-dichlorophenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione **1d** (0.3 g, 1.0 mmol) containing 1 M NaOH (30 mL) using multilamp reactor for 9 h, followed by usual work-up and chromatographic separation, afforded **2d**.Yield: 0.121 g (46%); mp 213–215 °C (lit.[21] mp 211–212 °C); UV: 242 nm (CH_3OH); IR (KBr): 1684, 1632, 1608, 1463 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.41 (s, 1H, C_6-CH), 7.24–7.66 (m, 5H, ArH), 8.44 (d, J = 8.8 Hz, 1H, C_4-ArH), 8.51 (d, J = 2.0 Hz, 1H, C_1-ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 82.5 (C_6-CH), 110.8, 116.9, 121.6, 125.0, 126.3, 128.1, 128.9, 129.8, 133.3, 137.8, 146.0, 150.2, 159.3 (C_{11}-CO). MS: *m/z* (%): 269 (M^+, 100), 271 (M+2, 34), 241 (12) [243 (4)], 234 (4), 213 (6) [215 (2)], 206 (20), 178 (30), 177 (16), 151 (14), 134.5 (M^{++}, 6), 125 (6), 115 (5), 101 (6), 89 (24).

4.3.5. 1-Chlorobenzoxazolo [3,2-*b*] isoquinolin-11-one 2e. The irradiation of *N*-(2,6-dichlorophenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione **1e** (0.3 g, 1.0 mmol) in acetonitrile (150 mL) containing 1 M NaOH (30 mL) for 10 h, using multilamp reactor, followed by usual work-up as mentioned above and chromatographic separation, furnished **2e**.Yield: 0.108 g (40%); mp 183–185 °C; UV: 240 nm (CH_3OH); IR (KBr): 1680, 1641, 1600, 1468 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.37 (s, 1H, C_6-CH), 7.26–7.67 (m, 4H, ArH), 7.82–8.00 (m, 2H, ArH), 8.46–8.54 (m, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 81.6 (C_6-CH), 108.6, 124.1, 124.7, 125.3, 126.9, 127.5, 128.5, 128.6, 131.5, 133.1, 134.6, 137.0, 150.0, 159.9 (C_{11}-CO). MS: *m/z* (%): 269 (M^+, 100), 271 (M+2, 33), 241 (16) [243 (6)], 234 (25), 213 (5) [215 (2)], 206 (18), 178 (25), 177 (16), 151 (10), 134.5 (M^{++}, 6), 125 (3), 115 (4), 101 (8), 89 (28). Anal. Calcd for $C_{15}H_8NO_2Cl$ (269.68): C, 66.80; H, 2.98; N, 5.19. Found: C, 66.57; H, 3.17; N, 5.39.

4.3.6. 3-Methylbenzoxazolo[3,2-*b*]isoquinolin-11-one 2f. The compound **2f** was obtained on irradiation of *N*-(2-bromo-4-methylphenyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione **1f** (0.3 g, 0.9 mmol) in acetonitrile (150 mL) containing 1 M NaOH (30 mL) for 7 h. Yield: 0.12 g (52%); mp 200–202 °C; UV: 236 nm (CH_3OH); IR (KBr): 1687, 1641, 1601, 1464 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.43 (s, 3H, CH_3), 6.38 (s, 1H, C_6-CH), 7.08–7.64 (m, 5H, ArH), 8.34 (d, J = 8 Hz, 1H, C_2-ArH), 8.45 (d, J = 8 Hz, 1H, C_1-ArH). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 22.1 (CH_3), 82.2 (C_6-CH), 110.8, 116.3, 121.9, 124.7, 125.1, 126.3, 128.1, 133.0, 137.1, 138.1, 147.8, 150.5, 159.5 (C_{11}-CO). MS: *m/z* (%): 249 (M^+, 100), 221 (8), 220 (9), 193 (7), 192 (12), 178 (3), 177 (2), 165 (8), 151 (13), 125 (5), 124.5 (M^{++}), 115 (6), 101 (4), 89 (13). Anal. Calcd for $C_{16}H_{11}NO_2$ (249.26): C, 77.09; H, 4.44; N, 5.61. Found: C, 76.92; H, 4.33; N, 5.82.

4.4. Irradiation of *N*-(2-chlorobenzyl)-1,2,3,4-tetrahydroisoquinoline-1,3-dione 1h

4.4.1. *N*-(2-Chlorobenzyl)-2-methylbenzamide 3. The irradiation of **1h** (0.3 g, 1.0 mmol) in acetonitrile (150 mL) containing 1 M NaOH (30 mL) was carried out (after flushing with nitrogen for 1 h) for 15 h in a multilamp reactor (254 nm). The completion of the reaction was checked by TLC; usual work-up and chromatographic separation using ethyl acetate-hexane mixture (1:9) afforded *N*-(2-chlorobenzyl)-2-methylbenzamide **3** (yield: 0.18 g, 69%; mp 100–102 °C).

Further, the compound **3** was confirmed with the authentic sample by mp, mixture mp and superimposable IR. The authentic sample was prepared by the addition of a benzene solution of 2-methylbenzoyl chloride (1.5 g, 9.7 mmol) to 2-chlorobenzyl amine (1.37 g, 9.7 mmol) in benzene (40 mL) containing a few drops of pyridine (yield = 1.6 g, 67%).

4.4.2. Isoquinolino[3,2-*b*[[1,3]benzoxazin-11-one 4. Irradiation of 0.3 g (1.0 mmol) of **1h** in acetonitrile containing 3 M NaOH (30 mL) was carried out for 12 h (after flushing with nitrogen for 1 h) in a multlamp reactor. After completion of the reaction (checked by TLC),

followed by usual work-up, the column chromatographic separation using petroleum ether-ethyl acetate (4:1) as eluant, afforded **4** (yield: 0.12 g, 47%; mp 210–212 °C). The spectral data of compounds **3** and **4** were reported earlier.[13]

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N,*N*,*N*′-Trialkyl-1,8-diaminonaphthalenes: convenient method of preparation from protonated proton sponges and the first X-ray information

V. A. Ozeryanskii,[a,*] A. F. Pozharskii,[a] M. G. Koroleva,[a] D. A. Shevchuk,[a] O. N. Kazheva,[b] A. N. Chekhlov,[b] G. V. Shilov[b] and O. A. Dyachenko[b]

[a]*Department of Organic Chemistry, Rostov State University, Zorge 7, 344090 Rostov-on-Don, Russian Federation*
[b]*Institute of Problems of Chemical Physics, Russian Academy of Sciences, Institutski 18, 142432 Chernogolovka, Moscow Region, Russian Federation*

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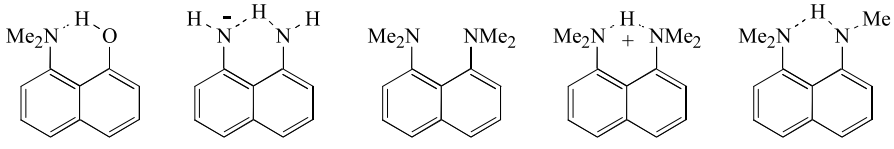
Abstract—A simple procedure for the synthesis of *N*,*N*,*N*′-trialkyl-1,8-diaminonaphthalenes is described. It consists in partial demethylation (dealkylation) of commercially available proton sponge [1,8-bis(dimethylamino)naphthalene] and some of its derivatives at heating with HBr–KI–DMF system. Limitation, scope and a possible mechanistic pathway for the reaction are discussed. For isomeric 8-dimethylamino-1-methylamino- and 1-dimethylamino-8-methylamino-4-nitronaphthalenes, X-ray measurements have been conducted. The first examples of complete realkylation reactions in the naphthalene proton sponges are reported.

1. Introduction

peri-Interactions of substituents in the derivatives of naphthalene and other polynuclear systems have been extensively investigated.[1] The importance of such interactions, along with the steric and electronic effects, has been attributed to intramolecular hydrogen bonds (IHB) of 'O–H···O', 'O–H···N' or 'N–H···N' types. The ease of their formation is responsible for a variety of conformational effects,[2] intramolecular acid catalysis,[3] changes in acid–base properties, often dramatic. For example, the IHB in 8-dimethylamino-1-naphthol (**1**) ($pK_a = 14.9$, H_2O, 25 °C) decreases the acidity of OH group by almost 6 powers of ten, when compared to 1-naphthol ($pK_a = 9.3$).[4] The enhanced NH-acidity of 1,8-diaminonaphthalene ($pK_a = 24.5$, DMSO, 25 °C) unlike simple arylamines ($pK_a = 28$–30) is also believed to be due to stabilization of the corresponding anion **2** via IHB.[5] The remarkable importance of IHB has long been recognized in the chemistry of 1,8-bis(dimethylamino)naphthalene (proton sponge, **3**) and its numerous analogues.[6] It was shown that the formation of IHB in cation **4**, in many aspects, is responsible for the unusually high basicity of this compound ($pK_a = 12.1$, H_2O, 25 °C).[7] Symmetry and low-barrier character of the N···H···N bond in the proton sponge cations attract considerable attention both from the standpoint of theory and modeling proton transfer processes in biological systems.[8] In this respect, the properties of hydrogen bridge in *N*,*N*,*N*′-trimethyl-1,8-diaminonaphthalene are intriguing to study. Earlier, a consideration of the IR[9] and NMR spectra,[10] including analysis of especially informative scalar $^{2H}J_{N,N}$ spin–spin constants,[11] demonstrated that this compound exists in solution as a chelate (**5**)



1 2 3 4 5

Keywords: Proton sponges; *N*,*N*,*N*′-Trialkyl-1,8-diaminonaphthalenes; Demethylation; Dealkylation; Realkylation; Intramolecular hydrogen bond; Nitronaphthalenes; Molecular and crystal structures.
* Corresponding author. Tel./fax: +7 8632975146; e-mail: vv_ozer2@chimfak.rsu.ru

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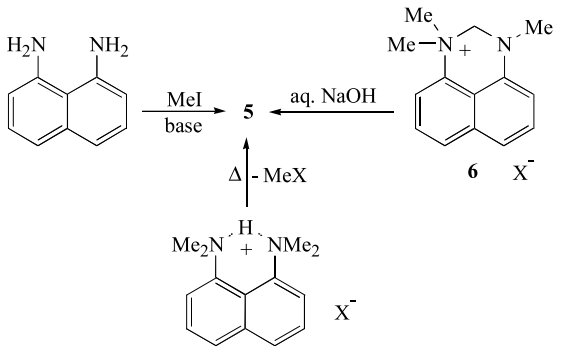
with flat NHMe and pyramidalized NMe_2 groups. Unfortunately, unlike compound **1**[12] and multiple proton sponge salts (**4**),[6,13] hitherto there was no information on the structure of *N*,*N*,*N*′-trialkyl-1,8-diaminonaphthalenes in the solid state. The present work describes a convenient method for the preparation and the first structural data on these compounds.

2. Results and discussion

2.1. Synthesis

Three general methods for the preparation of *N*,*N*,*N*′-trialkyl-1,8-diaminonaphthalenes are known in the literature: (1) alkylation of 1,8-diaminonaphthalenes with methyl iodide or dimethylsulphate in the presence of a base;[11,14] (2) alkaline fission of 1,1,3-trialkyl-2,3-dihydroperimidinium salts **6**;[15] (3) partial demethylation of the proton sponge.[14a,16] These are illustrated in Scheme 1 (compound **5** is given as an example).[17]



Scheme 1.

Though the first route is the least expensive and simple, it suffers from the formation of mono-, di- and tetraalkylation by-products. The second way, being very effective, includes multi-staged and time-consuming preparation of 2,3-dihydroperimidinium salts **6**. Considering the commercial accessibility of proton sponge **3**, we tuned our attention on a third method, which operates via thermal demethylation of proton sponge salts in the presence of highly polarizable nucleophiles of the type $PhSe^-$, PhS^-[16] or SCN^-.[14a] There are firm grounds to believe that this reaction runs through a classical S_N2-substitution mechanism. In the present investigation we have suggested and tested iodide ion as the nucleophile, since handling of thiophenol and selenophenol is unpleasant and requires the use of inert atmosphere,[16] and utilization of thiocyanate-anion is effective only at elevated temperatures (about 220 °C for 2 h), still providing a moderate yield of **5** (~50%).[14a]

In the course of a series of experiments with the proton sponge, and its *ortho*- and *para*-substituted derivatives (Table 1), it was found that the mixture of concentrated HBr (1 equiv) and KI (5 equiv) in boiling dimethylformamide possesses optimal dealkylation ability. Moreover, in this case one can avoid using an inert atmosphere (entry 1). The presence of an acid ensures transformation of proton sponge into the salt **4** with methyl groups bearing some positive charge and hence having electrophilic character (no reaction occurs with KI alone). During the course of the reaction, the chelating proton stabilizes the transition state so that it becomes closer to the reaction product. HBF_4, HCl and HI can be used in place of HBr acid, albeit with poorer results. $HClO_4$ cannot be used due to its higher oxidizing ability. It is arbitrary to use proton sponges directly in the form of salts, which excludes acid addition to the reaction mixture. Tetrafluoroborates, iodides and bromides are particularly suited, and though the latter are prone to form hydrates, this does not hamper the dealkylation process.

Since the iodide-anion is a nucleophile in this reaction, it is interesting to know whether the dealkylation will proceed under heating the proton sponge hydroiodide in DMF? Indeed, the reaction also takes place in this case, though the rate for full conversion of the substrate reduces (70 min of reflux). It was further established that bromide ion also has the ability to demethylate protonated proton sponge. Thus, boiling the salt **3**·HBr in DMF for 90 min produced compound **5** with 74% yield. This is much more efficient than the reported dealkylation of *N*,*N*-dialkylanilines at 150 °C in a great excess of gaseous HBr.[18] Use of an excess of KI (5 equiv) in DMF accelerates dealkylation, however changing KI to KBr reduces the rate (entries 2, 12). This is presumably due to the greater basicity of bromide ion and poor solubility of KBr in DMF.

Dimethylformamide also plays an important role in the dealkylation reaction. In fact, refluxing the proton sponge **3** in azeotropic aqueous HBr (126 °C) for an hour does not reveal any demethylation.

Based on the data in Table 1, the influence of the substrate structure on relative rate of the reaction can be considered. The latter is probably determined by the relative robustness and symmetry of the IHB in both the starting compound and the reaction product. Firstly, this is well displayed in the behavior of 2,3-bis(dimethylamino)naphthalene (**21**), and also in *N*,*N*,*N*′-trialkyl-1,8-diaminonaphthalenes, the cationic forms of which have rather weak IHB,[10,11,19] and therefore do not undergo demethylation (entries 15, 16). Other examples are compounds **3** and **10**, the first of which is demethylated faster and with higher yield (entries 1 and 4). It is known, that due to a tightening effect of the CH_2CH_2 *peri*-bridge, the nitrogen atoms in acenaphthene proton sponge **10** are more separated from each other, providing less symmetric and weakened IHB in the cation **10**·H^+.[17c,20] This is indicated by the X-ray data,[20] as well as by ^1H NMR spectra. For instance, the NH proton of cation **10**·H^+ resonates at δ_H 16.35 against 18.33 (DMSO-d_6) in cation **3**·H^+ (**4**).[17c] A similar tendency in the NH-proton chemical shifts is kept in the corresponding trimethyl substituted diamines **5** and **11** (Table 1).

Due to the electron-withdrawing effect of the NO_2 group, the IHB in cation **7**·H^+ is highly asymmetric. In dipolar aprotic solvents, including DMF, it is partially broken,[21] which should retard the rate of demethylation. This is indeed true (see Table 1, entry 3). The isomeric *N*,*N*,*N*′-trimethyl-1,8-diaminonaphthalenes **8** and **9** are formed here as the

Table 1. Synthesis of *N*,*N*,*N*′-trialkyl-diaminonaphthalenes and chemical shifts, δ_{NH}, in their ^{1}H NMR spectra[a]

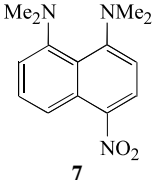
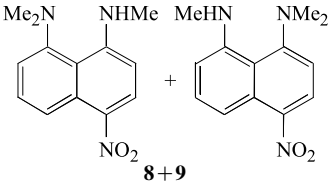
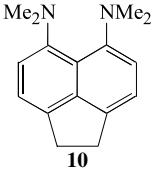
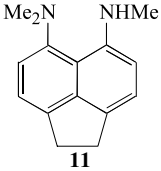
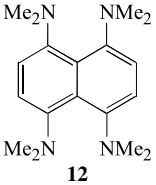
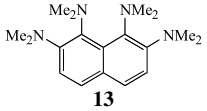
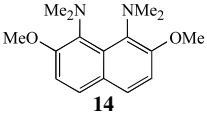
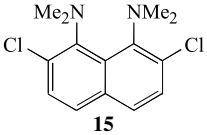
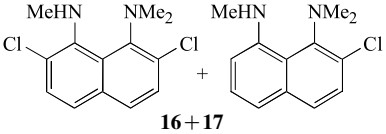
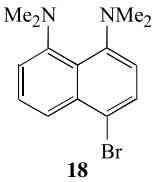
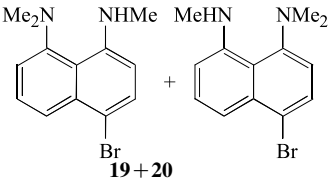
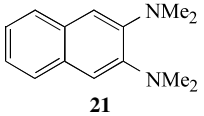
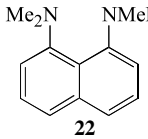
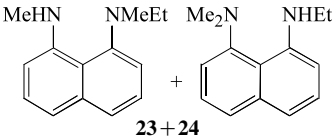
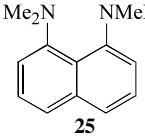
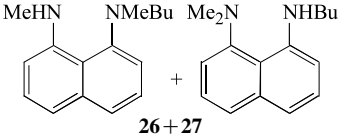
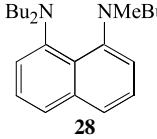
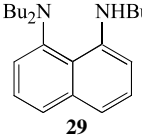
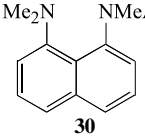
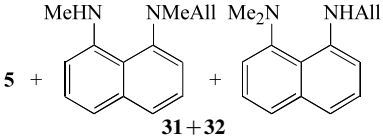
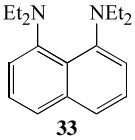
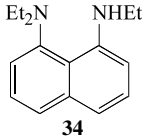
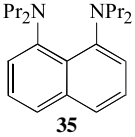
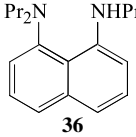
Entry	Starting compound	Product(s)	Reaction time (min)	Yield[b] (%)	δ_{NH}/$CDCl_3$ (ppm)
1	**3**	**5**	45	92	8.94
2[c]	**3**	**5**	120	89	—
3	 **7**	 **8**+**9**	120	63 (**8**) 34 (**9**)	10.84 (**8**) 8.50 (**9**)
4	 **10**	 **11**	60	72	8.00
5	 **12**	No reaction	—	—	—
6	 **13**	No reaction	—	—	—
7	 **14**	No reaction	—	—	—
8	 **15**	 **16**+**17**	1	26 (**16**) 9 (**17**)	9.66 (**16**) 9.38 (**17**)
9	**15**	**16**+**17**	15	69 (**16**) 21 (**17**)	—
10	**15**	**16**+**17**	40	54 (**16**) 31 (**17**)	—
11	**15**	**16**+**17**	60	28 (**16**) 52 (**17**)	—
12[c]	**15**	**16**	600	5	—
13	 **18**	**5** +  **19**+**20**	90	56 (**5**)[d] 25 (**19**)[d] 19 (**20**)[d]	— 9.06 (**19**) 9.00 (**20**)
14	**18**	**5**+**19**+**20**	180	73 (**5**)[d] 14 (**19**)[d] 9 (**20**)[d]	—
15	**5**	No reaction	—	—	—
16	 **21**	No reaction	—	—	—

Table 1 (*continued*)

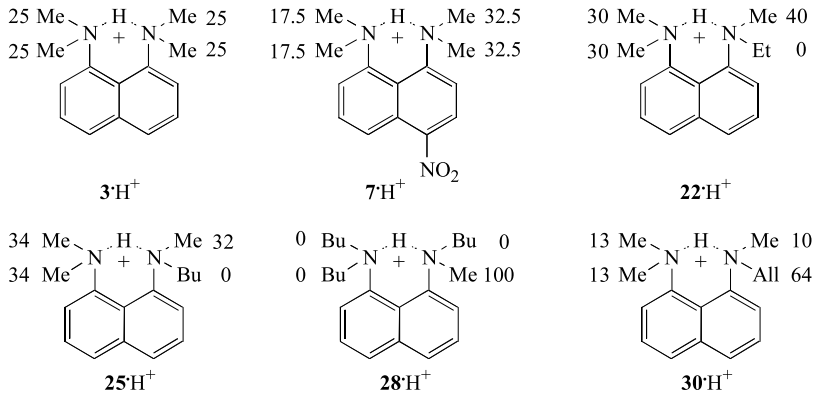
Entry	Starting compound	Product(s)	Reaction time (min)	Yield[b] (%)	$\delta_{NH}/CDCl_3$ (ppm)
17	 **22**	 **23+24**	60	60 (**23**)[d] 40 (**24**)[d]	9.36 (**23**) 9.00 (**24**)
18	 **25**	 **26+27**	60	68 (**26**)[d] 32 (**27**)[d]	9.35 (**26**) 9.12 (**27**)
19	 **28**	 **29**	90	84	9.63
20	 **30**	 **31+32**	7	64 (**5**)[d] 26 (**31**)[d] 10 (**32**)[d]	— 9.13 (**31**) 9.32 (**32**)
21	 **33**	 **34**	90	87	9.75
22	 **35**	 **36**	190	83	9.68

[a] All reactions were performed on a 0.4 mmol scale of the starting compound.
[b] Isolated yield.
[c] With KBr instead of KI.
[d] Determined by ^{1}H NMR of the reaction mixture; the compounds were not separated chromatographically.

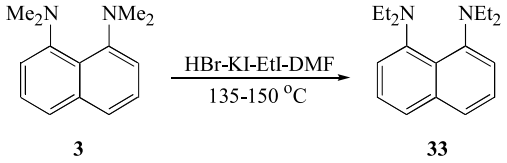
only products in a ~2:1 ratio, and with almost quantitative total yield. The prevalent formation of compound **8** can be explained by the enhanced stability of this nitrodiamine over its counterpart **9** due to stronger IHB and more effective conjugation between NO_2 and NHMe groups (see below the discussion of the X-ray diffraction data).

In the course of demethylation of the 4-bromo derivative **18** and 2,7-dichloride **15**, the main reaction pathway is complicated by partial dehalogenation, the extent of which increases with increasing reaction time (entries 8–14). Analysis of the data in Table 1 concerning relative yield of different products indicates that demethylation precedes dehalogenation. The mechanism of the latter was not studied here, though taking into account some literature precident,[22] one can assume that it consists of replacement of the chlorine or bromine atom by iodine, followed by successive elimination (reductive or via protodeiodination). In favor of this supposition is an additional experiment with **15**, in which potassium iodide was replaced by equivalent amount of KBr (entry 12). In this case, after prolonged reflux one can recycle up to 55% of proton sponge **15** and isolate no more than 5% of demethylation product **16**-monochloride **17** is not formed at all. The high conversion rate of 2,7-dichloride **15** is noticeable (1 min is enough for detection of **16** and **17**, entry 8). The nitrogen atoms in this compound, as well as in its cation, were shown to possess a high degree of planarization.[23] This should increase their electronegativity and significantly relieve the replacement of the CH_3 group.

At the same time, proton sponges **12**–**14**, distinguished by their sharply increased basicity,[6,13] does not produce any demethylation products (entries 5–7), though these compounds are highly strained in the form of free bases.[13] Apparently, the corresponding *N*,*N*,*N*′-trimethyl derivatives, owing to a strong electron-donating effect of



Scheme 2.



Scheme 3.

in the absence of *N*-methyl substituents in the proton sponge. This is illustrated by entries 21 and 22 for tetraethyl **33** and tetrapropyl **35** sponges. The bulkier the *N*-substituent is, the slower the reaction proceeds. The relative easiness for elimination of diverse *N*-alkyl groups, expressed via partial factors (%) for several proton sponge cations, is demonstrated in Scheme 2.

Table 2. Exhaustive realkylation of 1,8-bis(dimethylamino)naphthalene (**3**) with different alkyl iodides

Entry	RI	Final product(s)	Reaction time (h)	Yield (%)[a]	δ_{NH}/DMSO-d_6 of the corresponding proton sponge monocationic form (ppm)[b]
1	EtI	**33**	11	29	17.11
2	PrI	**35**+**36**	22	26 (**35**) 42 (**36**)	16.98
3	BuI	**29**	24	45	—

[a] Isolated yield.
[b] 18.33 for starting compound **3**, see Ref. 6.

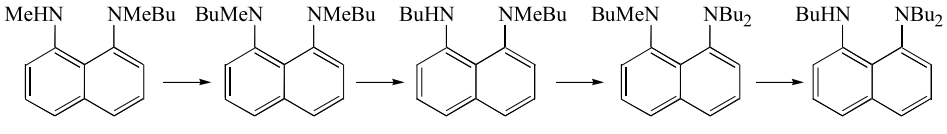
the NMe_2 and OMe substituents, are poor leaving groups.

A question on the nucleophilic elimination of bulkier *N*-alkyl groups from proton sponges seemed to deserve separate attention. This was evaluated by us for compounds **22**, **25**, **28**, **30**, **33** and **35**, which were allowed to react under standard conditions. It turned out that monoethyl **22** and monobutyl proton sponges **25** undergo only demethylation, which affects both the NMe_2 and NRMe groups to produce compounds **23**, **24** or **26**, **27**, respectively. Surprisingly, the presence of voluminous R-substituent in the NRMe group does not prevent demethylation; moreover, the latter is accelerated, especially for compound **22** (entries 17, 18). The reason can be ascribed to a greater +I-effect of the ethyl group in comparison with methyl, which favor the NH-proton in cation **22**·H^+ being shifted somewhat closer to the NEtMe-substituent. As expected, the demethylation of tributyl sponge **28** occurs regioselectively, providing tributyl derivative **29** in high yield (entry 19). In contrast, the monoallyl sponge **30** mostly loses the allyl substituent (entry 20), and the reaction, proceeding via the S_N1 or S_N2' mechanisms, requires ~10 min for its completion. Removal of the other alkyl groups can only be carried out

From the data above, an intriguing question as to whether it is possible to conduct exhaustive realkylation in the proton sponge series, say the transformation of **3** into **33** or **35**? We have established that this goal is attainable in one synthetic manipulation and with participation of only one equivalent of acid (Scheme 3, Tables 1 and 2).

So, IHB induced and H-bond-driven, the realkylation proceeds through dealkylation–quaternization steps and allows exchanging of the lower order alkyls by higher ones. The results for compound **3** are presented in Table 2. As far as we know, this simple reaction is still not resolved as a 'one-pot' process in the benzene series, and so is limited to the proton sponges.

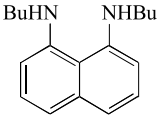
Apparently, the results of realkylation of **3** reflect a counterbalance of two main factors, namely steric hindrance and volatility of the corresponding alkyl halide. Thus, EtI is too volatile to provide high yields of the tetraethyl sponge (Table 2, entry 1) and BuI is too bulky to produce the tetrabutyl sponge, giving *N*-tributyl derivative **29** as the final product (entry 3). Indeed, when the reaction of **3** with HBr/KI/BuI/DMF was interrupted after 10 h, the ^{1}H NMR spectrum showed five compounds, namely **26**, **37**, **38**, **28**, and **29**, with predominance of the latter one.



26 (4%) **37** (22%) **38** (21%) **28** (13%) **29** (40%)

As it seen, 10 h are quite enough for fourfold demethylation and threefold quaternization in the case of BuI, though the complete conversion **3**→**29** requires additional 14 h and is realized with 45% efficiency (Table 2). Low relative amounts of proton sponges **28**, **37** (35%) over *N*-trialkyl derivatives **26**, **29**, **38** (65%) demonstrate that quaternization steps with higher alkyl halides are slower processes in comparison to demethylation.

Interestingly, on going from tetramethyl **3** to tetraethyl **33** and then to a tetrapropyl (**35**) proton sponge, the δ_{NH} value in the ^{1}H NMR of their protonated forms steadily decreases (δ_H 18.33→16.98, Table 2). A similar tendency, though in a lesser extent (9.75→9.63, Table 1) is observed for the series of trialkylated 1,8-diaminonaphthalenes **34**, **36** and **29**. In our opinion, this is connected with weakening of IHB owing to increasing steric hindrances. At the same time, electron-donating influence of the alkyl groups would promote additional shielding of the chelated proton.



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The structures of diamines **33**, **35**, **29** were also confirmed by their independent syntheses through exhaustive *N*-alkylation of 1,8-diaminonaphthalene in RI/KOH/HMPA mixtures (in DMF or DMSO the reaction proceeds worse).[24] This direct alkylation gives unambiguous results for compound **33** (yield 95–99% for 5–8 h).[24] In the case of propylation and butylation, even after 20–25 h, the reaction mixtures are complex and contain the following compounds as the main products: **35** (13–15%), **36** (48–52%); **29** (40–45%), **39** (20–23%). Thereby, the realkylation of proton sponges by means of demethylation–quaternization technique may have certain advantages over alkylation via *N*-anions, which for higher alkyls proceeds ineffectively.

2.2. Structural studies

For two of the synthesized compounds, namely nitrodiamines **8** and **9**, X-ray structural investigations have been conducted for the first time. Their results are given in Figures 1 and 2 and in Tables 3–5. The X-ray crystal structure of both samples is formed by one independent molecule of composition $C_{13}H_{15}N_3O_2$. Along *b* axis in the crystal, the molecules of **8** are packed into stacks with partial overlapping of naphthalene rings (Figs. 1 and 2). The distances between their planes in stacks are 3.43 and 3.48 Å; the dihedral angles between these planes in nearby stacks are 34.1°. The naphthalene rings orientation is of 'head-to-tail' type that is the nitro group of one molecule is situated above (below) the NHMe group of another one and vice versa (Table 5). Such orientation is easy to explain. The NMe_2 group in compound **8** is strongly pyramidalized and turned almost perpendicular to the bicycle plane. At the same time, the NHMe and NO_2 groups are near coplanar to the ring and there is effective through-conjugation between them. This comes to a significant contribution of the canonic structure **8b** and therefore to the shortening of C(7)–N(2) bond (crystallographic atom numbering, Table 4, Scheme 4), originating in orange color[21] and high dipole moment. According to PM3 semi-empirical calculations, the latter is

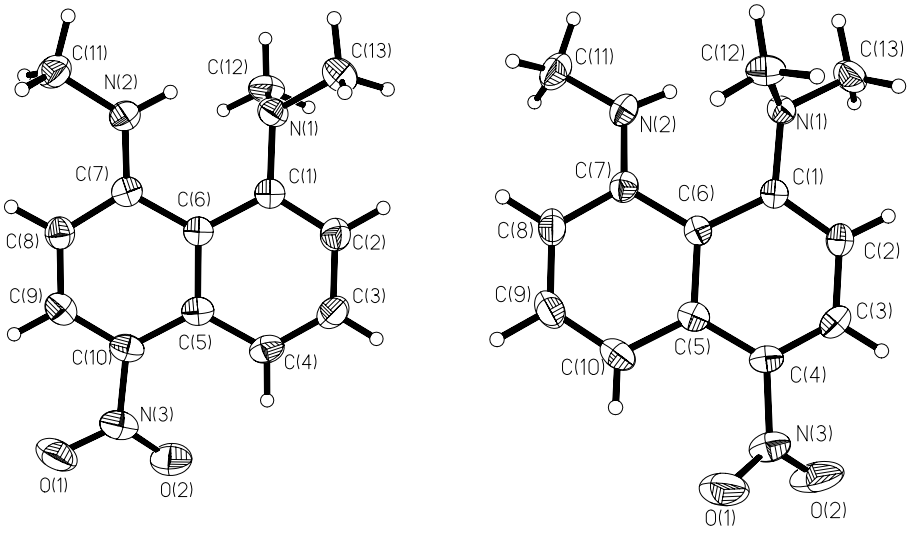


Figure 1. Structures of molecules **8** (left) and **9** (right) showing 30% probability ellipsoids of thermal motion and the atom numbering scheme.

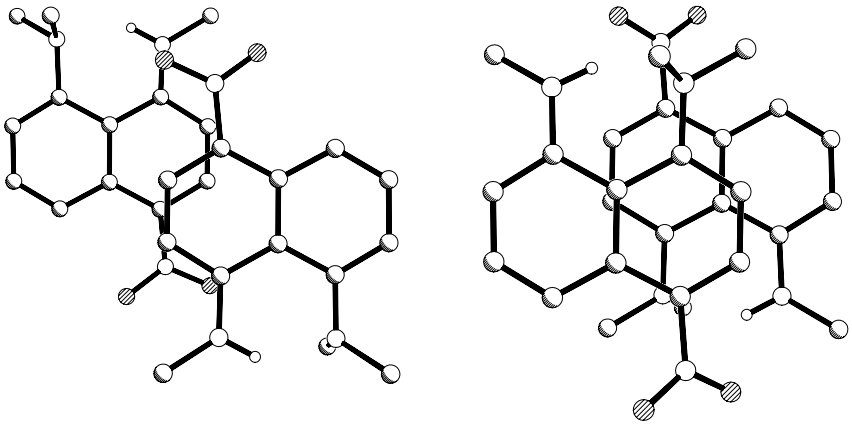


Figure 2. Fragments of crystal packing showing overlaying of pairs of molecules in stacks of **8** (left) and in parallel pairs of **9** (right).

Table 3. Crystal data and structure refinement for isomeric nitrodiaminonaphthalenes **8** and **9**

Parameter	**8**	**9**
Empirical formula	$C_{13}H_{15}N_3O_2$	$C_{13}H_{15}N_3O_2$
Formula weight	245.28	245.28
Temperature (K)	293(2)	293(2)
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/n$
a (Å)	10.486(2)	10.809(2)
b (Å)	7.224(1)	11.951(2)
c (Å)	16.326(3)	9.830(2)
α (deg)	90	90
β (deg)	105.35(2)	104.72(3)
γ (deg)	90	90
V (Å^3)	1192.6(4)	1228.1(4)
Z	4	4
D_{calcd} (g cm^{-3})	1.366	1.327
μ (mm^{-1})	0.095	0.092
F (000)	520	520
Reflections collected/unique	2171/2050	2170/2163
Rflns with $[F_0>4\sigma(F_0)]$	1750	1321
No. of refined parameters	209	209
$(2\theta)_{max}$ (deg)	49.94	50.12
Ranges:		
h	0–12	−12 to 12
k	0–8	−14 to 0
l	−19 to 18	−11 to 0
R-factor	0.034	0.041
CCDC deposit no.	251893	251894

Table 4. Selected crystallographic parameters for isomeric *N*,*N*,*N*′-trimethyl nitronaphthalenes **8** and **9** (lengths in Å, angles in deg, crystallographic atom numbering as in Fig. 1)

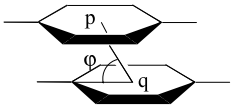
Parameter	**8**	**9**
N(1)···N(2)	2.650(1)	2.706(2)
N(2)–H	0.90(2)	0.89(3)
H···N(1)	1.90(2)	2.06(3)
∠N(2)–H···N(1)	139.1	127.6
N(1)–C(1)	1.441(2)	1.407(2)
N(2)–C(7)	1.341(2)	1.359(3)
∠NHMe-ring	2.2	11.8
∠NMe_2-ring	61.2	43.6
∠NO_2-ring	12.5	30.0
∑N(1)[a]	337.3	342.5
∑N(2)[a]	359.9	355.9

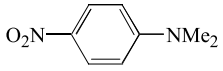
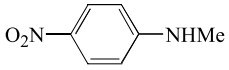
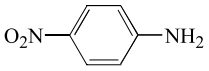
[a] Sum of CNC or CNH angles at that nitrogen atom.

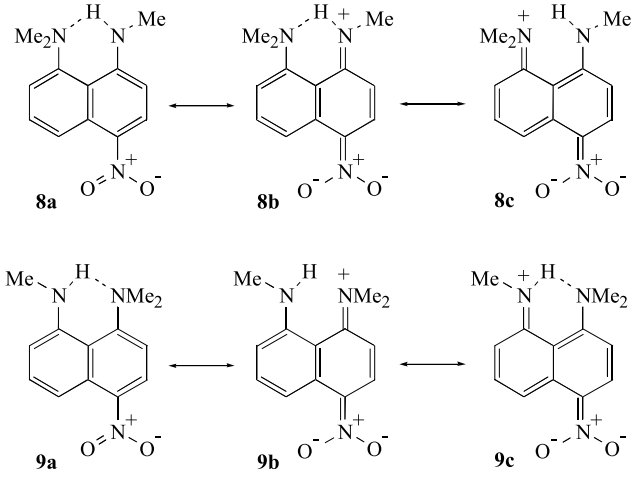
equal to 9.72 D (Table 6).[27] Thus, specific molecular packing in the crystals results from dipole–dipole interactions. Similar interactions are also characteristic for some other aromatic nitroamines, for example, compound **7** and 4-nitroanilines (see Table 5).

The molecular structure of **9** in comparison with **8** is more complex. The reason is that the conjugation of 1- and 4-substituents in the naphthalene system is more effective than that for substituents in positions 1 and 5. Therefore, in compound **9**, the NMe_2 group also tends to conjugate with the nitro function. This is reflected in its noticeable planarization, more coplanarity with the ring, shortening the C(1)–N(1) bond and in a whole set of other parameters, including enlargement of the distance N(1)···N(2) (Table 4). Accordingly, the degree of conjugation between

Table 5. Degree and type of overlapping of benzene rings in the closest pairs of different donor–acceptor substituted nitroarylamines in their crystals

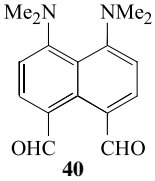


Compound	CCDC reference code	T (K)	r (p···q) (Å)	ϕ (deg)	Type of overlapping
8	—	RT	3.96	61	Head-to-tail
9	—	RT	3.75	76	Head-to-tail
7	ZOSKAT	RT	4.26	56	Head-to-tail
	DIMNAN01	110	3.87	61	Head-to-head
	FUXNAN	RT	4.02	61	Head-to-tail
	NANILI02	RT	3.83	62	Head-to-tail



Scheme 4.

Table 6. Dipole moments of some nitronaphthylamines and naphthalene proton sponges (in Debye units)

Compound	Calculated values			Experimental (C_6H_6, 25 °C)[a]
	AM1[b]	PM3[b]	Ab initio	
3	1.68	1.32	1.13[c]	1.19
8	9.44	9.72	—	—
9	8.28	8.24	—	—
 **40**	9.42	9.01	—	9.21

[a] Ref. 25.
[b] Calculated with HyperChem 6.0 program and with geometries based on cif-generated structures.
[c] Ref. 26.

the NO_2 and NHMe groups in **9** weakens, though still remains significant. Comparable contribution of bipolar structures **9b** and **9c** into the resonance hybrid results in the corresponding changes of crystal packing (Scheme 4). Unlike compound **8**, the molecules of **9** are packed in parallel pairs (similar to k-type packing of organic conductors)[28] and oriented by 'head-to-tail' type (Fig. 2, Table 5). The interplane distances between the aromatic rings in pairs are 3.52 Å; the dihedral angles between the rings of different pairs are 52.3°. It should be stressed that the degree of naphthalene rings overlapping in **9** is distinctively higher than in **8** and in other *p*-nitroarylamines, presented in the Cambridge Structural Database (Table 5). As the measure of such overlapping, we have picked up the distance p···q between the centers of "eclipsing" benzene rings, and also the angle ϕ, showing their horizontal offset comparatively each other. Obviously, the lesser the distance p···q and bigger ϕ, the stronger the rings overlapping. More effective overlapping between the aromatic rings in **9** allows to understand, why this compound, in spite of a smaller dipole moment (8.24 D, method PM3, see Table 6) and approximately the same position of long-wave absorption maximum in hexane [λ_{max}=427 nm (log ε 3.6) for **9** and 426 nm (log ε 3.9) for **8**],[21] appears in crystals deeper in color (maroon) than the isomeric nitrodiamine **8** (orange). It is clear that this coloration is caused by intermolecular electron transfer in crystals resulting in auto-π-complexes. Like other similar compounds with high dipole moment and with trend to formation of auto-π-complexes, for example, **7** and dialdehyde **40**, the isomeric nitrodiamines **8** and **9** have well observable metallic luster.

As for the N–H···N hydrogen bond in these two nitro compounds, it is rather weak, especially in **9**, where it is very asymmetric and with low degree of linearity (Table 4). Apart from this, the hexagon N(1)C(1)C(6)C(7)N(2)H(12) is deviated essentially out of flat conformation. For example, in molecule **9**, the dispositions of atoms from the mean plane of the specified hexagon are 0.23 Å for H(12), 0.22 Å for N(1) and 0.13 Å for C(7). The dihedral angle of the hexagon to the plane of bicycle C(1)C(2)···C(10) is equal to 12.9°. The above cited NMR data (see also Table 1 and

Section 3) are also evident for weak hydrogen bridge, which therefore retains in solutions of *N*,*N*,*N*′-trialkyl-1,8-diaminonaphthalenes.

3. Experimental

3.1. General

The ^{1}H NMR spectra were recorded with a Bruker DPX-250 instrument at 250 MHz using tetramethylsilane as internal reference. The IR spectra were registered on a Specord IR-75 spectrometer. Column chromatography was performed using Al_2O_3 or silica gel L 40/100 μm (Chemapol). The progress of reactions and the purity of products were monitored by TLC on Al_2O_3 and Silufol plates; development with iodine vapor. The melting points were determined in a sealed capillary using a PTP device and were not corrected. Nothing special were undertaken to control the purity and water contents in DMF, as well as to protect the reaction mixtures from air-oxygen. Proton sponge **3** was used as received (Lancaster).

The X-ray diffraction studies were performed on an Enraf-Nonius CAD-4 (for **8**) and KM-4 KUMA DIFFRACTION (for **9**) diffractometers using $\omega/2\theta$ scanning and graphite monochromated Mo-K_α radiation. The crystal structures were solved by direct methods followed by Fourier synthesis with SHELXS-97 and refined by the full-matrix least-squares methods for all non-hydrogen atoms with SHELXL-97 software packages.[29] The coordinates of H-atoms were found experimentally. General experimental details concerning the crystal structure determination are given in Table 3. Selected bond lengths, non-valent interatomic distances, and angles are summarized in Table 4.

3.2. Dealkylation of protonated proton sponges

General procedure. To a solution of the corresponding proton sponge (0.4 mmol) in 5 ml of DMF, solid KI (0.332 g, 2.0 mmol) and 46% aqueous HBr (0.05 ml, 0.4 mmol) were added. The resulting suspension was refluxed for the time specified in Table 1, then cooled to ambient temperature and poured into water (50 ml). The product(s) of dealkylation was (were) extracted with hexanes or benzene (3×3 ml), the organic phase was dried over Na_2SO_4, the solvent was removed, and the residue was chromatographed on alumina or silica gel if necessary (see below) to give pure compounds with the yields indicated in Table 1.

3.2.1. 1-Dimethylamino-8-methylaminonaphthalene (5). Beige oil or crystalline solid with mp 30–31 °C and with the same properties as has the pattern prepared by other methods.[15a,30] This could be additionally purified by elution with hexanes through a short column of Al_2O_3. ^{1}H NMR ($CDCl_3$) δ ppm: 2.76 (s, 6H, NMe_2), 2.96 (d, 3H, NMe), 6.41 (bd, 1H, H-7), 7.03 and 7.13 (both dd, 2H, H-5 and H-2), 7.29 and 7.30 (both t, 2H, H-6 and H-3), 7.49 (dd, 1H, H-4), 8.94 (bs, 1H, NH, exchangeable with D_2O); $J_{NH,NMe}$=4.77 Hz, $J_{2,3}$=7.33 Hz, $J_{3,4}$=8.06 Hz, $J_{2,4}$=1.10 Hz, $J_{5,6}$=8.06 Hz, $J_{6,7}$=7.70 Hz, $J_{5,7}$=1.10 Hz.

3.2.2. 8-Dimethylamino-1-methylamino-(8) and 1-dimethylamino-8-methylamino-4-nitronaphthalenes (9). The title compounds were prepared as indicated above as a mixture and separated on silica gel with chloroform elution. This allows isolating first **8** and then **9** with the same properties as the authentic samples have (See Ref. 17a).

3.2.3. 5-Dimethylamino-6-methylaminoacenaphthene (11). Brownish oil or crystalline solid with mp 39–40 °C;[15a] purification method as for **5**. ^{1}H NMR ($CDCl_3$) δ ppm: 2.73 (s, 6H, NMe_2), 2.96 (bs, 3H, NMe), 3.27 (s, 4H, CH_2CH_2), 6.38 (d, 1H, H-7), 7.10 (m, 3H, H-3, H-4, H-8), 8.00 (bs, 1H, NH); $J_{7,8}$=7.72 Hz.

3.2.4. 2,7-Dichloro-1-dimethylamino-8-methylamino-(16) and 2-chloro-1-dimethylamino-8-methylaminonaphthalenes (17). The title compounds were prepared as indicated above as a mixture and were separated further on silica gel with chloroform elution, which allows collecting first **17** and then **16** with the next properties. **16**: colorless crystals with mp 45–47 °C (from *n*-octane). Found: C, 58.19; H, 5.07; Cl, 26.62%. Calcd for $C_{13}H_{14}Cl_2N_2$: C, 58.01; H, 5.24; Cl, 26.34%. IR ($CHCl_3$) ν cm^{-1}: 3180 (N–H). ^{1}H NMR ($CDCl_3$) δ ppm: 2.99 (s, 6H, NMe_2), 3.08 (bs, 3H, NMe), 7.18 (d, 1H, H-5), 7.30 (d, 1H, H-3), 7.34 (d, 1H, H-6), 7.52 (d, 1H, H-4), 9.66 (bs, 1H, NH); $J_{3,4}$=8.87 Hz, $J_{5,6}$=8.48 Hz. **17**: colorless oil. Found: C, 66.14; H, 6.58; Cl, 15.32%. Calcd for $C_{13}H_{15}ClN_2$: C, 66.52; H, 6.44; Cl, 15.10%. IR ($CHCl_3$) ν cm^{-1}: 3240 (N–H). ^{1}H NMR ($CDCl_3$) δ ppm: 2.97 (bs, 9H, NMe_2+NMe), 6.43 (dd, 1H, H-7), 6.98 (dd, 1H, H-5), 7.26 (d, 1H, H-3), 7.30 (t, 1H, H-6), 7.50 (d, 1H, H-4), 9.38 (bs, 1H, NH); $J_{3,4}$=8.48 Hz, $J_{5,6}$=8.10 Hz, $J_{6,7}$=7.33 Hz.

3.2.5. 1-Diethylamino-8-ethylaminonaphthalene (34). The title compound was obtained as brownish oil with the properties revealed by authentic sample[15a] and purified with the method applied for **5**. ^{1}H NMR ($CDCl_3$) δ ppm: 1.05 and 1.39 (both t, 6H and 3H, CH_2CH_3), 3.08 and 3.25 (both m, 4H and 2H, CH_2CH_3), 6.40 (bd, 1H, H-7), 7.02 and 7.15 (both dd, 2H, H-5 and H-2), 7.28 (m, 2H, H-3 and H-6), 7.54 (dd, 1H, H-4), 9.75 (bs, 1H, NH); $J_{2,3}$=7.33 Hz, $J_{3,4}$=8.10 Hz, $J_{2,4}$=1.16 Hz, $J_{5,6}$=8.10 Hz, $J_{6,7}$=7.72 Hz, $J_{5,7}$=0.77 Hz.

3.2.6. 1-Dipropylamino-8-propylaminonaphthalene (36). The title compound was prepared as light-brown oil and purified as compound **5**; does not freeze even under −30 °C. Found: C, 80.39; H, 10.05%. Calcd for $C_{19}H_{28}N_2$: C, 80.23; H, 9.92%. IR (liquid film) ν cm^{-1}: 3195 (N–H). ^{1}H NMR ($CDCl_3$) δ ppm: 0.83 and 1.08 (both t, 6H and 3H, Pr), 1.47, 1.76, 2.97, 3.17 (all m, 4H, 2H, 4H, 2H, Pr), 6.39 and 7.00 (both bd, 2H, H-7, H-5), 7.16 (dd, 1H, H-2), 7.27 (m, 2H, H-3, H-6), 7.52 (dd, 1H, H-4), 9.68 (bs, 1H, NH); $J_{2,3}$=7.72 Hz, $J_{3,4}$=8.10 Hz, $J_{2,4}$=1.15 Hz, $J_{5,6}$=7.33 Hz, $J_{6,7}$=7.72 Hz.

3.3. Synthesis of proton sponges and model compounds

Except for commercially available 1,8-bis(dimethylamino)-naphthalene (**3**), all other proton sponge compounds exploited in the present work were synthesized following published procedures: **7**,[21] **10**,[17b] **12**,[31] **13**, **14**,[32] **15**,[33] **18**,[15b]

33.[24] The latter compound (**33**) has in our hands mp 29–31 °C and therefore is not an oily substance as it was described. Proton sponge isomer **21** was prepared from 2,3-diaminonaphthalene according to method[34] and compound **22** was obtained in the reaction of **5** with EtI.[15a] Following the latter procedure with BuI and AllBr, **5** gave in high yields compounds **25** and **30**, respectively, and **29** gave **28** on heating with MeI. Propyl sponge **35** was synthesized in analogy with tetraethyl derivative **33**.[24] The properties of new compounds are as next.

3.3.1. 2,3-Bis(dimethylamino)naphthalene (21). Light-beige oil. Yield 87%. Found: C, 78.30; H, 8.62%. Calcd for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47%. ^{1}H NMR ($CDCl_3$) δ ppm: 2.89 (s, 12H, NMe_2), 7.18 (s, 2H, H-1, H-4), 7.26 (m, 2H, H-6, H-7), 7.64 (m, 2H, H-5, H-8). **21**·$HClO_4$: colorless needles with mp 203–204 °C (decomp. from EtOAc). Found: C, 53.29; H, 6.18; Cl, 12.05%. Calcd for $C_{14}H_{19}ClN_2O_4$: C, 53.42; H, 6.09; Cl, 11.86%. ^{1}H NMR (CD_3CN) δ ppm: 3.04 (s, 12H, NMe_2), 7.65 (m, 2H, H-6, H-7), 7.99 (m, 2H, H-5, H-8), 8.21 (s, 2H, H-1, H-4), 10.1 (very broad s, 1H, NH).

3.3.2. 1-Butylmethylamino-8-dimethylaminonaphthalene (25). Colorless oil. Yield 68%. Found: C, 80.12; H, 9.37%. Calcd for $C_{17}H_{24}N_2$: C, 79.64; H, 9.43%. ^{1}H NMR ($CDCl_3$) δ ppm: 0.85 (t, 3H, Bu), 1.20, 1.52, 2.7–3.1 (all m, 6H, Bu), 2.77, 2.79, 2.82 (bs, s and s, 9H, NMe), 6.93 (bm, 2H, H-2, H-7), 7.27 (m, 2H, H-3, H-6), 7.35 (m, 2H, H-4, H-5). **25**·HI: yellowish crystals with mp 218–222 °C (decomp. from C_6H_6:MeCN—2:1). Found: C, 53.01; H, 6.69; I, 32.84%. Calcd for $C_{17}H_{25}IN_2$: C, 53.13; H, 6.56; I, 33.02%. ^{1}H NMR (DMSO-d_6) δ ppm: 0.84 (t, 3H, Bu), 1.1–1.8 (m, 4H, Bu), 3.10, 3.12, 3.17 (all d, 9H, NMe), 7.75 (m, 2H, H-3, H-6), 8.11 (m, 4H, H-2, H-7, H-4, H-5), 17.92 (bs, 1H, NH), a signal of N–CH_2 (Bu) protons overlapped with NMe signals; $J_{NH,1\text{-}NMe}=2.59$ Hz, $J_{NH,8\text{-}NMe}=2.10$ Hz.

3.3.3. 8-Butylmethylamino-1-dibutylaminonaphthalene (28). Light-beige oil. Yield 93%. Found: C, 81.27; H, 10.32%. Calcd for $C_{23}H_{36}N_2$: C, 81.12; H, 10.66%. ^{1}H NMR ($CDCl_3$) δ ppm: 0.82 (m, 9H, Bu), 1.1–1.7 (m, 12H, Bu), 2.78 (s, 3H, NMe), 3.09 (bm, 6H, N–CH_2), 6.93 (m, 2H, H-2, H-7), 7.26 (m, 2H, H-3, H-6), 7.35 (m, 2H, H-4, H-5). **28**·$HClO_4$: colorless oil. Found: C, 62.38; H, 8.54; Cl, 7.90%. Calcd for $C_{23}H_{37}ClN_2O_4$: C, 62.64; H, 8.46; Cl, 8.04%. ^{1}H NMR (DMSO-d_6) δ ppm: 0.87 (m, 9H, Bu), 1.2–1.9 (m, 12H, Bu), 3.09 (d, 3H, NMe), 3.19 (m, 6H, N–CH_2), 7.75 (m, 2H, H-3, H-6), 8.03 (m, 2H, H-2, H-7), 8.13 (m, 2H, H-4, H-5), 17.37 (bs, 1H, NH); $J_{NH,NMe}=1.15$ Hz. The hydroiodide, hydrobromide and *p*-bromobenzoate salts of this proton sponge are also liquid at room temperature.

3.3.4. 1-Allylmethylamino-8-dimethylaminonaphthalene (30). Colorless oil. Yield 97%. Found: C, 80.05; H, 8.24%. Calcd for $C_{16}H_{20}N_2$: C, 79.96; H, 8.39%. ^{1}H NMR ($CDCl_3$, 40 °C) δ ppm: 2.80 (s, 6H, NMe_2), 2.83 (s, 3H, NMe), 3.59 (bs, 2H, N–CH_2), 5.11, 5.17, 5.95 (all m, 3H, All), 6.98 (m, 2H, H-2, H-7), 7.31 (m, 2H, H-3, H-6), 7.39 (m, 2H, H-4, H-5). At 20 °C the 3.59 ppm signal splits into two broad singlets and 2.80 peak becomes very broad. **30**·HBr: light-cream crystals with mp 195–197 °C (from C_6H_6:MeCN—2:1). Found: C, 59.63; H, 6.72; Br, 24.59%. Calcd for $C_{16}H_{21}BrN_2$: C, 59.82; H, 6.59; Br, 24.87%. ^{1}H NMR (DMSO-d_6) δ ppm: 3.10, 3.17, 3.22 (all d, 9H, NMe), 4.06 (m, 2H, N–CH_2), 5.25, 5.37, 5.78 (all m, 3H, All), 7.74 (m, 2H, H-3, H-6), 8.09 (m, 2H, H-2, H-7), 8.16 (m, 2H, H-4, H-5), 18.00 (bs, 1H, NH); $J_{NH,1\text{-}NMe}=1.52$ Hz, $J_{NH,8\text{-}NMe}=3.06$ Hz.

3.3.5. 1,8-Bis(diethylamino)naphthalene perchlorate (33·$HClO_4$). Light-beige crystals with mp 104–105 °C (decomp. at 214–217 °C, from EtOH). Found: C, 58.46; H, 7.23; Cl, 9.32%. Calcd for $C_{18}H_{27}ClN_2O_4$: C, 58.29; H, 7.34; Cl, 9.56%. ^{1}H NMR (DMSO-d_6) δ ppm: 1.12 (t, 12H, CH_2*Me*), 3.35–3.70 (m, 8H, N–CH_2), 7.75 (t, 2H, H-3, H-6), 8.14 (bd, 2H, H-2, H-7), 8.14 (bd, 2H, H-4, H-5), 17.11 (bs, 1H, NH); $J_{NH,N-CH}=2.27$, 2.92 Hz, $J_{2,3}=7.77$ Hz, $J_{3,4}=8.10$ Hz.

3.3.6. 1,8-Bis(dipropylamino)naphthalene (35). Colorless crystals with mp 52.5–54.5 °C. Yield 15%. Found: C, 80.79; H, 10.62%. Calcd for $C_{22}H_{34}N_2$: C, 80.92; H, 10.50%. ^{1}H NMR ($CDCl_3$) δ ppm: 0.75 (t, 12H, Pr), 1.2–1.7 (m, 8H, Pr), 3.09 (t, 8H, N–CH_2), 6.91 (bd, 2H, H-2, H-7), 7.23 (bt, 2H, H-3, H-6), 7.33 (bd, 2H, H-4, H-5); $J_{2,3}=7.33$ Hz, $J_{3,4}=8.10$ Hz. **35**·HBr: colorless oil. Found: C, 64.71; H, 8.90; Br, 19.49%. Calcd for $C_{22}H_{35}BrN_2$: C, 64.85; H, 8.66; Br, 19.61%. ^{1}H NMR (DMSO-d_6) δ ppm: 0.86 (t, 12H, Pr), 1.2–1.7 (m, 8H, Pr), 3.15–3.65 (m, 8H, N–CH_2), 7.74 (t, 2H, H-3, H-6), 7.99 (bd, 2H, H-2, H-7), 8.13 (bd, 2H, H-4, H-5), 16.98 (bs, 1H, NH); $J_{2,3}=7.44$ Hz, $J_{3,4}=8.09$ Hz.

3.4. Realkylation of proton sponges and direct *N*-butylation of 1,8-diaminonaphthalene

General procedure for realkylation of 1,8-bis(dimethylamino)naphthalene (**3**). A solution consisting of proton sponge **3** (0.086 g, 0.4 mmol), KI (0.332 g, 2.0 mmol), DMF (8 ml), alkyl iodide (0.2–1.0 ml) and 46% aqueous HBr (0.05 ml, 0.4 mmol) was refluxed for the time indicated in Table 2 so that the internal temperature was maintained at 135–150 °C and with repeated addition of the alkyl iodide, if necessary. The reaction mixture was then slowly cooled to ambient temperature and poured into water (55 ml). The aqueous phase was made strongly basic with KOH and the product of realkylation was taken up into hexanes (4× 3 ml). The organic phase was dried over anhydrous K_2CO_3, the solvent was removed, and the residue was chromatographed on basic alumina with hexane elution to give pure compounds with the yields specified in Table 2.

Direct N-butylation of 1,8-diaminonaphthalene. A suspension consisting of 1,8-diaminonaphthalene (1.27 g, 8 mmol), powdered KOH (2.24 g, 40 mmol), HMPA (24 ml), butyl iodide (8 ml, 70 mmol) was heated to 120–130 °C for 24 h under nitrogen with stirring. After cooling to room temperature, dilution with water (100 ml) and basifying with KOH to pH >11, the products of *N*-alkylation were extracted with EtOAc (4×25 ml) and the organic phase was thoroughly washed with water and dried over Na_2SO_4. After the solvent was removed, the residue was chromatographed on Al_2O_3 with PhMe elution. This allowed collecting the next compounds in the order of elution.

3.4.1. 8-Butylamino-1-dibutylaminonaphthalene (29). Yellow crystals darkening on light and air, mp 29–33 °C. Yield 42%. Found: C, 80.67; H, 10.64%. Calcd for $C_{22}H_{34}N_2$: C, 80.92; H, 10.50%. IR (liquid film) ν cm^{-1}: 3205 (N–H). ^1H NMR ($CDCl_3$) δ ppm: 0.83 and 0.99 (both t, 6H and 3H, Bu), 1.15–1.58 (m, 10H, Bu), 1.71, 2.98, 3.18 (all m, 2H, 4H, 2H, Bu), 6.37 and 6.98 (both bd, 2H, H-7, H-5), 7.13 (dd, 1H, H-2), 7.26 (m, 2H, H-3, H-6), 7.50 (dd, 1H, H-4), 9.63 (bs, 1H, NH); $J_{2,3}=7.72$ Hz, $J_{3,4}=8.10$ Hz, $J_{2,4}=1.16$ Hz, $J_{5,6}=8.10$ Hz, $J_{6,7}=7.33$ Hz.

3.4.2. 1,8-Bis(butylamino)naphthalene (39). Pinky-beige crystals darkening on light and air, mp 55–56 °C. Yield 21%. Found: C, 80.17; H, 9.36%. Calcd for $C_{18}H_{26}N_2$: C, 79.95; H, 9.69%. IR (CCl_4) ν cm^{-1}: 3350, 3280 (N–H). ^1H NMR ($CDCl_3$) δ ppm: 1.00 (t, 6H, Bu), 1.50 and 1.70 (both m, 8H, Bu), 3.09 (t, 4H, NCH_2), 5.49 (bs, 2H, NH), 6.56 (dd, 2H, H-2, H-7), 7.17 (dd, 2H, H-4, H-5), 7.24 (t, 2H, H-3, H-6); $J_{2,3}=6.95$ Hz, $J_{3,4}=8.10$ Hz, $J_{2,4}=1.16$ Hz.

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27. In order to estimate the reliability of calculated values for dipole moments of **8** and **9**, Table 6 contains also the results of calculations according to the methods AM1 and PM3. They are compared with the similar data for parent proton sponge **3** and its 4,5-diformyl derivative **40**, for which experimental values are also available. As it seen, for dialdehyde **40**, there is a good agreement (deviation is less than 3%) between the experiment and the theory (both methods, AM1 and PM3, are almost equally acceptable). In the case of **3**, the discrepancy for AM1 is inadmissibly big (~30%), while for the PM3 method it is much less (~10%). Therefore, the discussion of results is based on the PM3 data. It should be emphasized that,

at the same time, the best correspondence in estimating the dipole moment of **3** gave ab initio calculations (see Ref. 26).

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Reinvestigation of the conversion of epoxides into halohydrins with elemental halogen catalysed by thiourea

Mirosław Soroka* and Waldemar Goldeman

Politechnika Wrocławska, Instytut Chemii Organicznej, Biochemii i Biotechnologii, Wybrzeże Wyspiańskiego 27, PL-50370 Wrocław, Poland

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Abstract—In contrast to a previous literature report, thiourea is not a catalyst in the ring opening reaction of epoxides by means of bromine or iodine. Instead, thiourea reacts with the halogen to give a complex mixture of products, among them hydrogen halogenides, which are in fact the real epoxide ring opening reactants. The presence of water is crucial in this reaction.

In 2003, a paper was published in this journal[1] describing the ring opening reaction of epoxides to halohydrins by means of bromine or iodine, in the presence of thiourea as a catalyst. The authors also discussed the mechanistic details of this reaction and proposed a four-step mechanism, where the thiourea plays an essential role as a catalyst. Their proposal was supported by UV spectra, and by cited literature precedents. The authors neither isolated nor confirmed the presence of the catalyst, namely thiourea, in the reaction mixture after reaction. Moreover, the reaction of thiourea with bromine or iodine is well-known. It was described for the first time by Claus[2a] in 1875, and was subsequently repeated and studied many times.[2b–g] Generally, the distribution of the products depends strongly on the conditions of the reaction. Under anhydrous conditions in organic solvent, the main product is the formamidine disulfide dihydrohalogenide. For example, King and Ryden[2f] applied this product as a reactant for the preparation of thiazoles. However, under stronger conditions (in an excess of halogen or in the presence of water) the reaction gives a complex mixture of products which, according to McGovan,[2c] contains cyanamide, hydrogen halogenide, sulfur and even sulfuric acid.

Under such circumstances, it is unlikely that thiourea could be a catalyst in the reaction described by Sharghi and Eskandari,[1] and could survive in the presence of such strong oxidizing and electrophilic reagents like bromine or iodine. Therefore, we decided to reinvestigate this reaction.

When we repeated the reaction of methyloxirane[3] with iodine in the presence of 10 mol% of thiourea as described by Sharghi and Eskandari,[1] we identified the iodohydrins by means of ^{1}H NMR spectroscopy (see Section 1.1.1), but with low yield (only about 30%), and a considerable amount of unreacted iodine. By titration of the residual iodine, we estimated the stoichiometry of the reaction as about 1 mol of iodine per 2 mol of thiourea. This means that the thiourea is not a catalyst but just the reagent.

A similar reaction of methyloxirane with bromine in the presence of 10 mol% of thiourea (Section 1.1.2) gave us only 32% yield of distilled bromohydrins and a huge amount of a dark unidentified residue. When we changed the molar ratio of bromine to thiourea to 1 to 2 (Section 1.1.3), we observed almost quantitative yield of crystalline formamidine disulfide dihydrobromide, and no bromohydrins at all.

When we applied 2 mol of thiourea and 1 mol of iodine (Section 1.1.4), and then we added an excess of water, the iodine disappeared in a few minutes, and we found in the reaction mixture more than 70% yield of iodohydrins, and the yellow precipitate, which was identified by elemental analysis and IR spectrum as elemental sulfur, in more than 60% yield. The presence of water seems to be essential to complete the reaction of iodine with thiourea.

Our findings are shown by the sequence in Scheme 1.

In conclusion, we could not reproduce the Sharghi and Eskandari protocol.[1] The only role the thiourea plays in their protocol is to generate the hydrogen halogenide which

Keywords: Oxiranes; Ring opening; 2-Halogenoalkanols; Bromohydrins; Iodohydrins.
* Corresponding author. Tel.: +48 71 3202404; fax: +48 71 3284064; e-mail: miroslaw.soroka@pwr.wroc.pl

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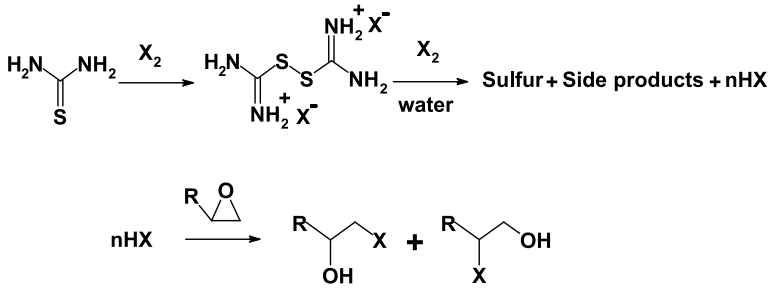

Scheme 1.

reacts in situ with the epoxide. When we reinvestigated this reaction we found that the thiourea reduces molecular halogen to the hydrogen halogenide, via formamidine disulfide dihydrohalogenides. It appears that the author's extensive discussion and the final conclusions concerning the catalytic effect of thiourea are in error.

Furthermore, we would not advise use of this protocol for the preparation of halohydrins from epoxides. However, if elemental halogen must be used as a reactant for epoxide ring opening, we advise use of our procedure based on generation of hydrogen halogenide in the halogenation of active aromatics, developed some time ago, and recently described.[4]

1. Experimental

1.1. General

NMR spectra were recorded by Mr. Rafał Kozicki on a Bruker Avance 300 MHz spectrometer locked on deuterium from solvent. Chemical shifts (δ [ppm]) were calculated from chemical shift of deuterium lock and were not calibrated. FTIR spectra were measured on Perkin Elmer 2000 spectrometer in KBr pellets (1/200) by Mrs. Elzbieta Mróź. Mass spectra were measured on HP8542 mass detector coupled with HP8542 gas chromatograph, by Dr. Andrzej Nosal. Elemental analyses were done by Mrs. Czesława Andrzejewska. Melting points were determined on the Boetius microscope with electrical hot plate and were corrected. The structures of all compounds were derived from ^{1}H NMR spectra. The required methyloxirane was acquired from local manufacturer. All reagents and solvents were of commercial quality and purchased from local supplier (POCh Gliwice).

1.1.1. Experiment 1. The reaction of iodine with methyloxirane in the presence of 10 mol% amount of thiourea—a reinvestigation. Methyloxirane (1.3 g, 22 mmol) was added to a stirred suspension of thiourea (0.15 g, 2.0 mmol) in acetonitrile (25 mL) at about 20 °C. Next, a solution of iodine (5.1 g, 20 mmol) in acetonitrile (25 mL) was added dropwise (30 min) to the above mixture at the same temperature. The dark reaction mixture was stirred 1 h, then water was added in one portion at the same temperature, and next a solution of $Na_2S_2O_3$*$5H_2O$ (10 g, 40 mmol) in water (100 mL) was added. Almost immediately the reaction mixture decolorized. The mixture was extracted with dichloromethane (1×50, then 2×20 mL), organic phases were collected and dried over Na_2SO_4 (20 g), filtered and evaporated under vacuo from warm water bath (below 40 °C) to give oily residue (1.3 g, about 35%) identified and assayed by means of NMR as the mixture of iodohydrins–1-iodopropan-2-ol and 2-iodopropanol in 74/26 ratio (calculated from integrals of methyl groups at 1.30 and 1.89 ppm, respectively), and traces of unidentified impurities.

When an excess of iodine was titrated by 1.00 M of $Na_2S_2O_3$ in water, as much as about 90% of unreacted iodine was found remained after reaction.

1.1.2. Experiment 2. The reaction of bromine with methyloxirane in the presence of 10 mol% amount of thiourea—a reinvestigation. Methyloxirane (5.8 g, 100 mmol) was added to a stirred suspension of thiourea (0.76 g, 10 mmol) in acetonitrile (50 mL) at 10 °C (ice-water bath). Next, a solution of bromine (5.1 mL, 100 mmol) in acetonitrile (20 mL) was added dropwise (30 min) to the above mixture at the same temperature. The reaction mixture was stirred to reach the temperature about 20 °C, and then overnight. The next day, a 0.10 mL of the reaction mixture was taken, evaporated, and dissolved in a 0.50 mL of $CDCl_3$, and NMR spectrum was measured, on which only ca 30% of bromohydrins were found. Then, the whole reaction mixture was evaporated under vacuo from warm water bath (below 40 °C) to give oily residue which was distilled under vacuo (bulb to bulb) from water bath to give 4.4 g of bromohydrins (32% yield), and about 12 g of unidentified thick oily residue. The distillate was identified and assayed by means of NMR as a mixture of bromohydrins–1-bromopropan-2-ol and 2-bromopropanol in 75/25 ratio (calculated from integrals of methyl groups at 1.26 and 1.66 ppm, respectively).

1.1.3. Experiment 3. The reaction of bromine with methyloxirane in the presence of stoichiometric amount of thiourea. Methyloxirane (2.9 g, 50 mmol) was added to a stirred suspension of thiourea (3.8 g, 50 mmol) in acetonitrile (50 mL) at 10 °C (ice-water bath). Next, a solution of bromine (1.3 mL, 25 mmol) in acetonitrile (10 mL) was added dropwise (30 min) to the above mixture at the same temperature. Immediately white crystals precipitated. The reaction mixture was stirred to reach the temperature about 20 °C, and additionally half an hour. The precipitate was filtered off, washed with acetonitrile, and dried on air to give 7.8 g of product (about 100% of yield), identified as formamidine disulfide dihydrobromide by comparison with authentic sample[2f] by means of IR spectrum, and

elemental analyses. The filtrates after isolation of formamidine disulfide dihydrobromide contained no bromohydrins.

1.1.4. Experiment 4. The reaction of iodine with methyloxirane in the presence of stoichiometric amount of thiourea, and then with addition of water. Methyloxirane (2.3 g, 40 mmol) was added to a stirred mixture of thiourea (1.5 g, 20 mmol) in acetonitrile (50 mL) at about 20 °C. Next, a solid iodine (2.5 g, 10 mmol) was added in a few portions to the above mixture at the same temperature. The reaction mixture was stirred for half an hour more at the same temperature, then water (50 mL) was introduced in one portion, and stirring was continued till the reaction mixture decolorized. The mixture was extracted with dichloromethane (1×50, then 2×20 mL), organic phases were collected and dried over Na_2SO_4 (20 g), filtered and evaporated under vacuo from warm water bath (below 40 °C) to give oily residue (2.8 g, about 76%) identified and assayed by means of NMR as the mixture of iodohydrins–1-iodopropan-2-ol and 2-iodopropanol in 89/11 ratio (calculated from integrals of methyl groups at 1.31 and 1.89 ppm, respectively), and traces of unidentified impurities. From inhomogenous water phase the yellow precipitate was isolated by filtration, dried on air to give 0.20 g of elemental sulfur (87% purity, 63% of yield) identified by combustion to H_2SO_4 and titration, and by comparison of IR spectrum to those from the library as well as from a measurement of pure element.

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Hetero Diels–Alder reaction: a novel strategy to regioselective synthesis of pyrimido[4,5-*d*]pyrimidine analogues from Biginelli derivative

Pratibha Sharma,* Ashok Kumar, Nilesh Rane and Vamsi Gurram

School of Chemical Sciences, Devi Ahilya University, Indore Takshila Campus, Khandwa Road, Indore, MP 452 017, India

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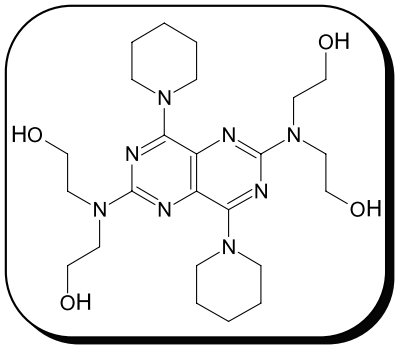
Abstract—A number of potent pyrimido[4,5-*d*]pyrimidine analogues have been efficiently synthesized by hetero Diels–Alder cycloaddition of 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester, a Biginelli compound with *N*-arylidine-*N*′-methylformamidines and *N*-arylidine guanidine in dry toluene. Structures of the newly obtained cycloadducts were established on the basis of elemental and spectral (IR, NMR and Mass) data. The molecular mechanism of the observed cycloaddition reaction has been investigated theoretically by means of PM3 semiempirical method. Transition state structure determinations and activation energy calculations have shown the preference for the *endo* approach over the *exo* approach of dienophile towards the diene fragments used, which is consistent with the experimental results. The studied cycloadditions proceed via an asynchronous concerted mechanism. It was demonstrated that FMO theory could reasonably predict the relative reactivities between dienes as well as indicating that these reactions belong to normal Diels–Alder type cycloadditions.

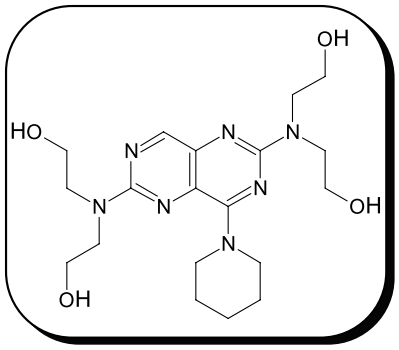
1. Introduction

In recent years, the hetero Diels–Alder (HDA) reaction has emerged as an elegant protocol for the construction of six membered heterocyclic systems.[1] HDA's ability to generate four new contiguous stereogenic centers in a single laboratory operation, with the regio- and stereo-chemical outcomes being predicted using orbital symmetry considerations enhances its synthetic utility. Moreover, an increasingly growing number of heterodienes and heterodienophiles broaden the scope of HDA reactions as a mainstay of many heterocycle and natural product syntheses.[2]

Among them, pyrimido[4,5-*d*]pyrimidine, a condensed heterocycle, represents an attractive target due to the interesting pharmacological activities of these molecules as regards the modulation of antitumor drug acitivity,[3]



Dipyridamole (RA-8)



Mopidamole (RA233)

Figure 1. Prototype of pyrimido[4,5-*d*]pyrimidine and its derivative.

Keywords: Hetero Diels–Alder cycloadditions; Pyrimido[4,5-*d*]pyrimidines; Biginelli compound; Dienophile; Semiempirical; PM3.
* Corresponding author. Tel.: +91 731 2460208; fax: +91 731 2470372; e-mail: drpratibhasharma@yahoo.com

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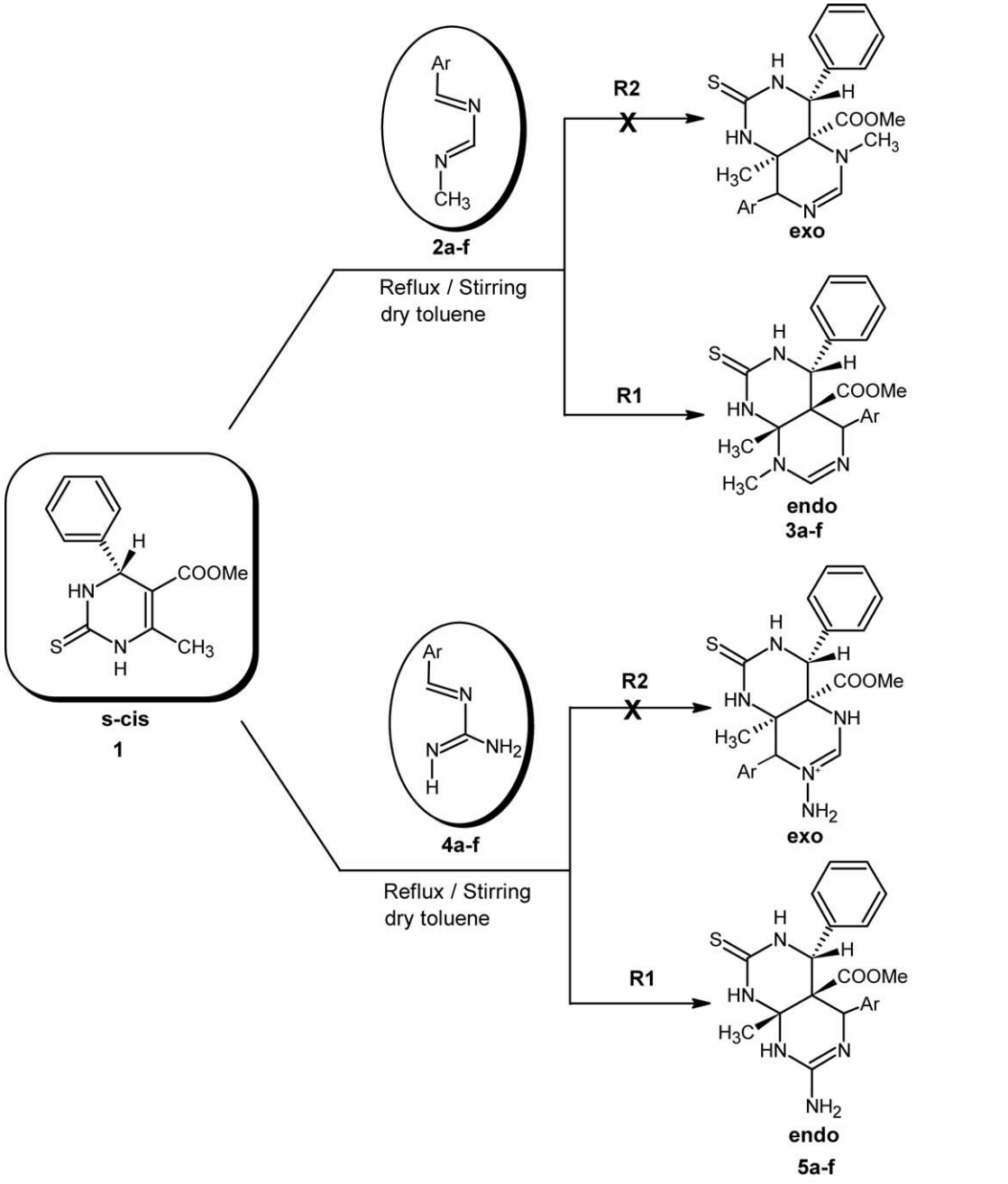
antioxidant (lipid peroxidation inhibitors),[4] antiviral,[5] and potent inhibitory action on the tyrosine kinase domain of epidermal growth factor receptor,[6] 5-phosphoribosyl-1-pyrophosphate synthetase[7] and dihydrofolate reductase.[8] Again, pyrimido[4,5-*d*]pyrimidine prototype dipyridamole (RA-8) and its derivative mopidamole (RA-233) (Fig. 1) are clinically approved effective cardiovascular[9] and anti-neoplastic agents.[10] Thus, the efficient and novel synthesis of such compounds is of prime interest and represents a highly pursued target.

Buoyed from the aforementioned information and in continuation of our previous work on versatile syntheses of heterocycles,[11–15] we herein report for the first time a novel and expeditious strategy to prepare a number of potent pyrimido[4,5-*d*]pyrimidine analogues based on the $[\pi 4_s + \pi 2_s]$ cycloaddition reaction, considering the 5,6 double bond of the Biginelli compound as a dienophile in a one pot synthesis. In addition, the transition state energy of conformers responsible for producing the selective stereo-isomers is also discussed.



2 & 4	a	b	c	d	e	f
Ar	C_6H_4	4-ClC_6H_4	4-OHC_6H_4	4-$OCH_3C_6H_4$	4-$C_2H_5C_6H_4$	4-$CH_3C_6H_4$

Scheme 1. Synthetic route for pyrimido[4,5-*d*]pyrimidine derivatives.

Table 1. Kinetic results of [4+2]cycloaddtions of dienophile (**1**) with dienes

Entry	Diene[a]	Reaction conditions	Time to completion[b] (h)	Yield[c] (%)
1	**2a**	Reflux	15	72
2	**2b**	Reflux	10	76
3	**2c**	Stirring/RT	6	79
4	**2d**	Stirring/RT	4	82
5	**2e**	Reflux	19	73
6	**2f**	Reflux	9	80
7	**4a**	Reflux	17	70
8	**4b**	Reflux	11	74
9	**4c**	Stirring/RT	8	77
10	**4d**	Stirring/RT	7	80
11	**4e**	Reflux	20	71
12	**4f**	Reflux	10	78

[a] 2 equiv of diene.
[b] Monitored by TLC/HPLC.
[c] Isolated yield.

2. Results and discussion

2.1. Synthesis

The most promising methods for the construction of pyrimido[4,5-*d*] pyrimidine nucleus include multistep syntheses, starting from 1,3-disubstituted-5-cyanouracils[16] or from polymer bound 2-(alkylsulfanyl)-4-amino-pyrimidine-5-carbonitrile.[17] However, these approaches involve relatively long synthetic pathways or the use of stoichiometric amounts of expensive resin as a polymer support. Our synthetic strategy, utilizing 4-phenyl-tetrahydropyrimidine-5-carboxylate derivative with substituted methyl formamidine and guanidine affords an unprecedented and facile one-pot synthesis of pyrimido[4,5-*d*]pyrimidine analogues in good to excellent yields (Scheme 1).

The 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester (**1**) herein considered as dienophile in our synthetic plan, was readily obtained by Biginelli reaction of benzaldehyde, methyl acetoacetate and

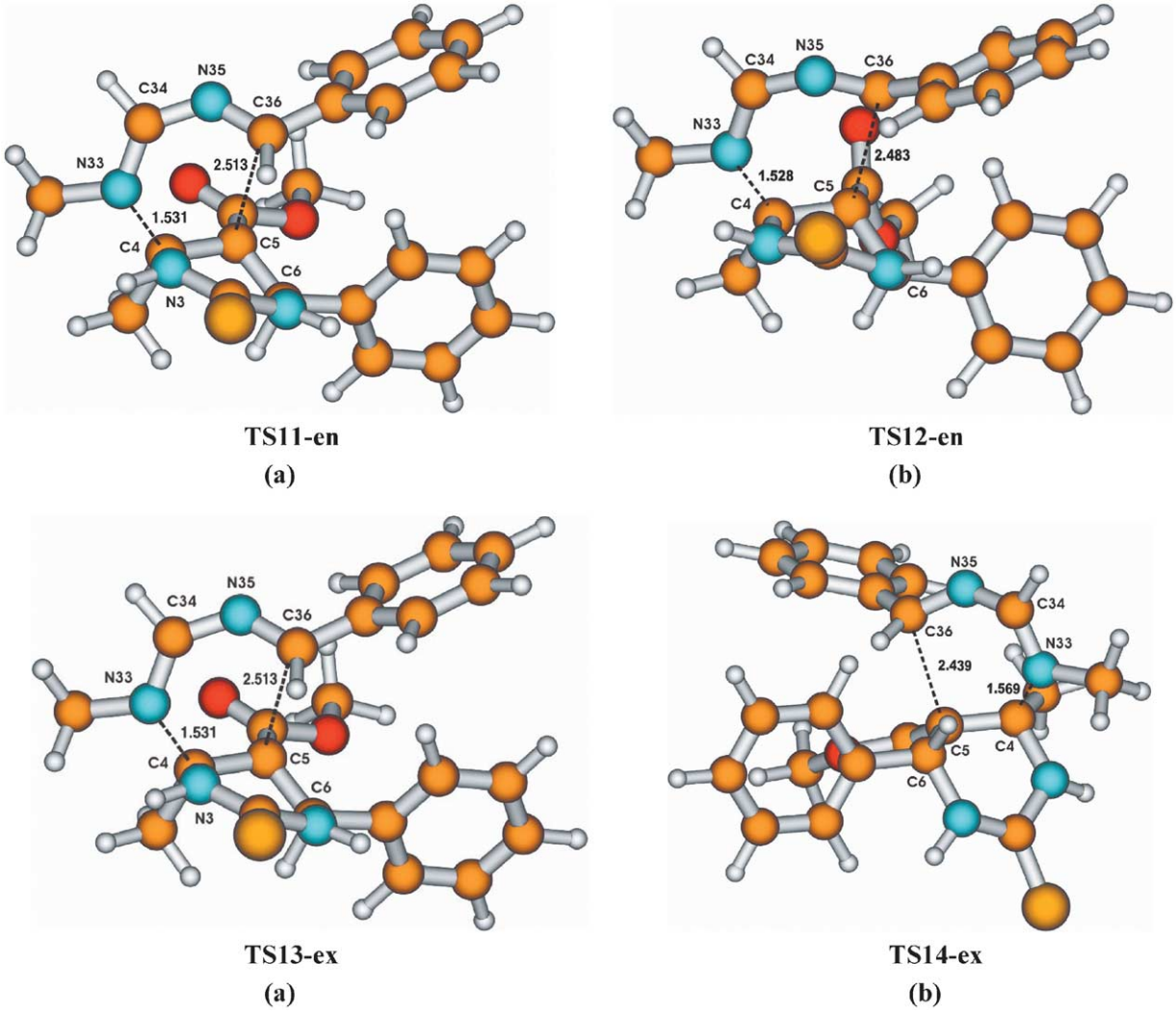


Figure 2. Transition state structures corresponding to regioisomer **1** for the [4+2]cycloaddition reaction between **1** and **2a**. (a) *trans*-approach; (b) *cis*-approach.

thiourea in refluxing ethanol. The reaction proceeds more efficiently when carried out using microwave irradiation. *N*-arylidine-*N*′-methylformamidines (**2a–f**) and *N*-arylidine guanidine (**4a–f**) were used as the diene component in the course of the reaction, which in turn were efficiently obtained from Schiff base condensation of appropriate aldehydes with *N*-methyl formamidine and guanidine, respectively. The hetero Diels–Alder reaction was carried out by refluxing/stirring these dienes (**2a–f**, **4a–f**) with dienophile (**1**) in a 2:1 molar ratio in anhydrous toluene for the required time (Table 1) in order to obtain the cycloadducts (**3a–f**, **5a–f**) bearing different substituents in 70–82% yields.

In summary, the pyrimidine nucleus, fused to the tetrahydropyrimidine ring was constructed by cycloaddition of the C–C fragment, derived from the Biginelli compound with C–N–C–N fragment of methyl formamidine and/or guanidine derivatives.

2.2. Computational studies

To unravel the understanding of mechanistic details of these cycloaddtions, we have performed the systematic quantum chemical investigations on representative HDA reactions between dienophile (**1**) and dienes (**2a** and **4a**). The SCF calculations at RHF level using PM3 semiempirical method[18] as incorporated in MOPAC 6.0 package[19] were employed.

An exhaustive exploration of the potential energy surfaces (PESs) for [4+2] cycloadditions under consideration furnished the relevant stationary points for reactants, transition state structures (TSs), and cycloadducts. Further, full geometry optimization was carried out by eigen-value following routine[20] using PM3 Hamiltonian. Finally, the nature of each stationary point was determined by diagonalizing the Hessian matrix to determine the number of imaginary frequencies (one for local minima and zero for saddle point).

In order to explicitly verify that each saddle point leads to two putative minima, the IRC pathways[21] have also been traced from all the transition states appearing on the cycloaddition energy surface profile.

Though the dienophile (**1**) can exist in two different conformations (*s-cis* or *s-trans*), which may bind with the diene, however, only *s-cis* approach has been considered to be the most probable one as previous ab initio (HF/3–21G)

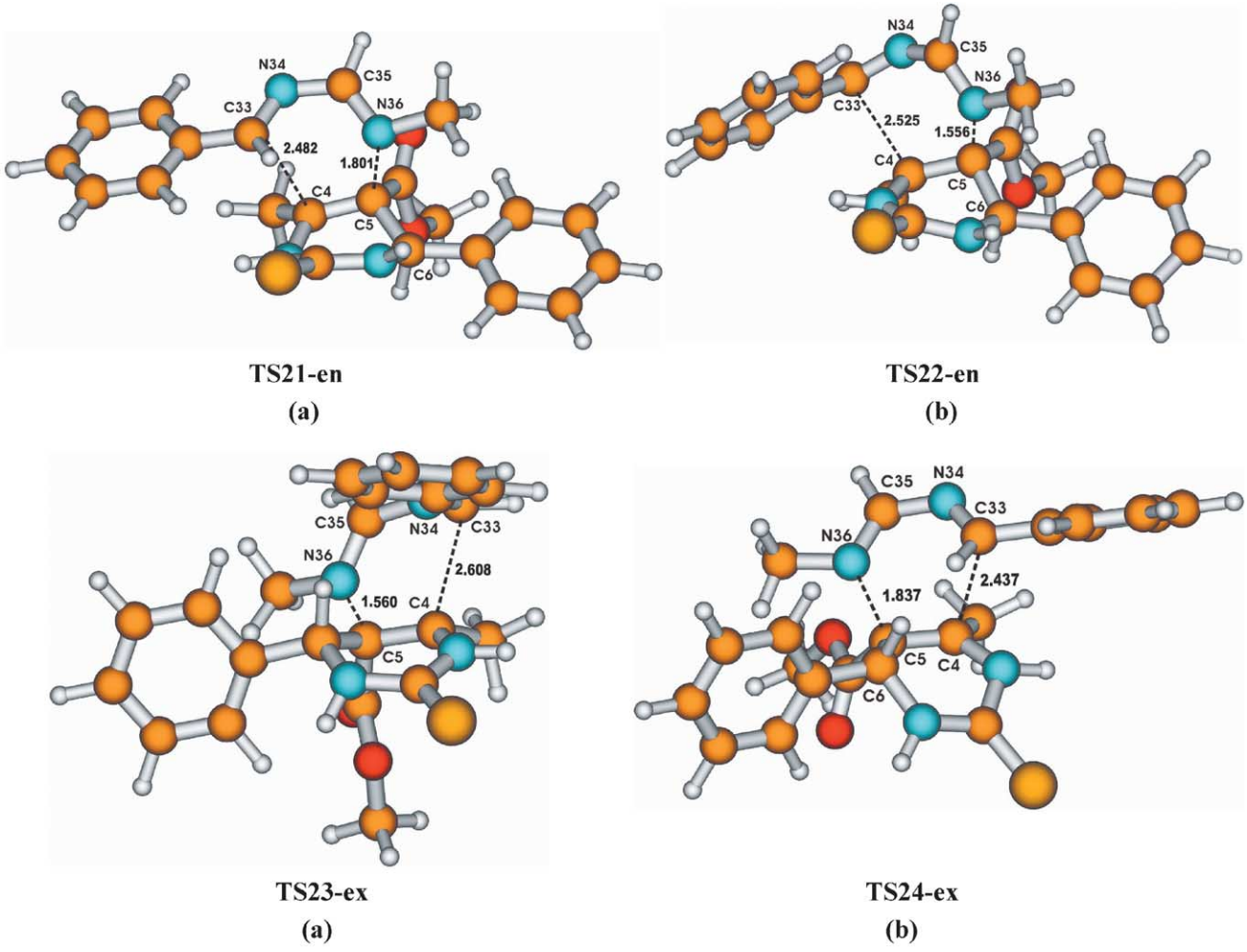


Figure 3. Transition state structures corresponding to regioisomer **2** for the [4+2]cycloaddition reaction between **1** and **2a**. (a) *trans*-approach; (b) *cis*-approach.

and semiempirical molecular orbital calculations (AM1, PM3) and X-ray crystallographic studies corroborate *s-cis* as the lower energy conformer.[22]

The results from these theoretical studies suggest that the observed cycloadditions can take place along a concerted mechanism through two reactive channels viz. *endo* and *exo* in order to generate two regioisomers (R1 and R2). Therefore, total eight transition states and eight cycloadducts have been located and characterized on PES for each representative HDA reaction corresponding to two regioisomers; two face of attack on diene (*cis* and *trans* approach) and exo/endo possibilities. For these reactions, we have labeled the transition structures as TS11–TS14 (R1) (Fig. 2) and TS21–24 (R2) (Fig. 3) for attack of **2a** on **1**. Correspondingly, TS31–TS34 (R1) (Fig. 4) and TS41–44 (R2) (Fig. 5) represent the transition states for reaction of **1** with **4a**. From these TSs, the related minima corresponding to the final cycloadducts are labeled as P11–44, respectively (Table 2).

Heat of formation for all the four TSs corresponding to R2 as compared to R1 is exceptionally large. Moreover, the *trans*-selectivity can be explained on the basis of data pertaining to Table 2, according to which, the heat of formation belonging to the endo-*trans* (TS11, 87.03 kcal mol^{-1}) conformer is 2.22 kcal mol^{-1} less than that of the endo-*cis* congener (TS12, 89.25 kcal mol^{-1}). On the other hand, the energy difference between the exo-*trans* (TS13) and exo-*cis* (TS14) conformers is 0.51 kcal mol^{-1}, but the mean difference between the energy of two sets of TSs are considerable, that is, PM3 calculated heat of formation of transition state belonging to the endo-*trans* (TS11-en, 87.03 kcal mol^{-1}) conformer is 1.53 kcal mol^{-1} less than that of the *exo* congener (TS13-ex, 88.51 kcal mol^{-1}) for the cycloaddition of **1** with **2a**. Similarly, TS31-en

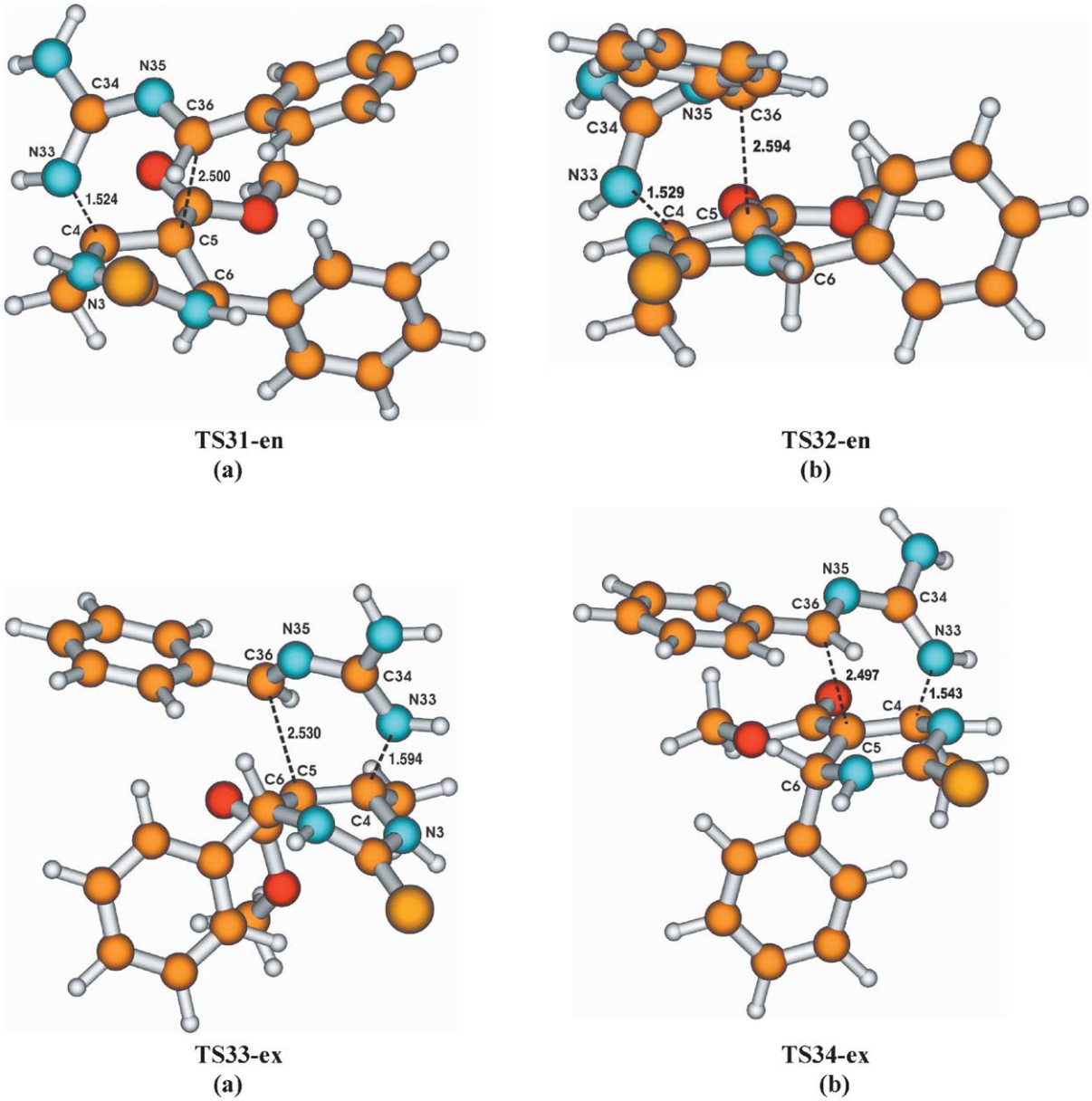


Figure 4. Transition state structures corresponding to regioisomer **1** for the [4+2]cycloaddition reaction between **1** and **4a**. (a) *trans*-approach; (b) *cis*-approach.

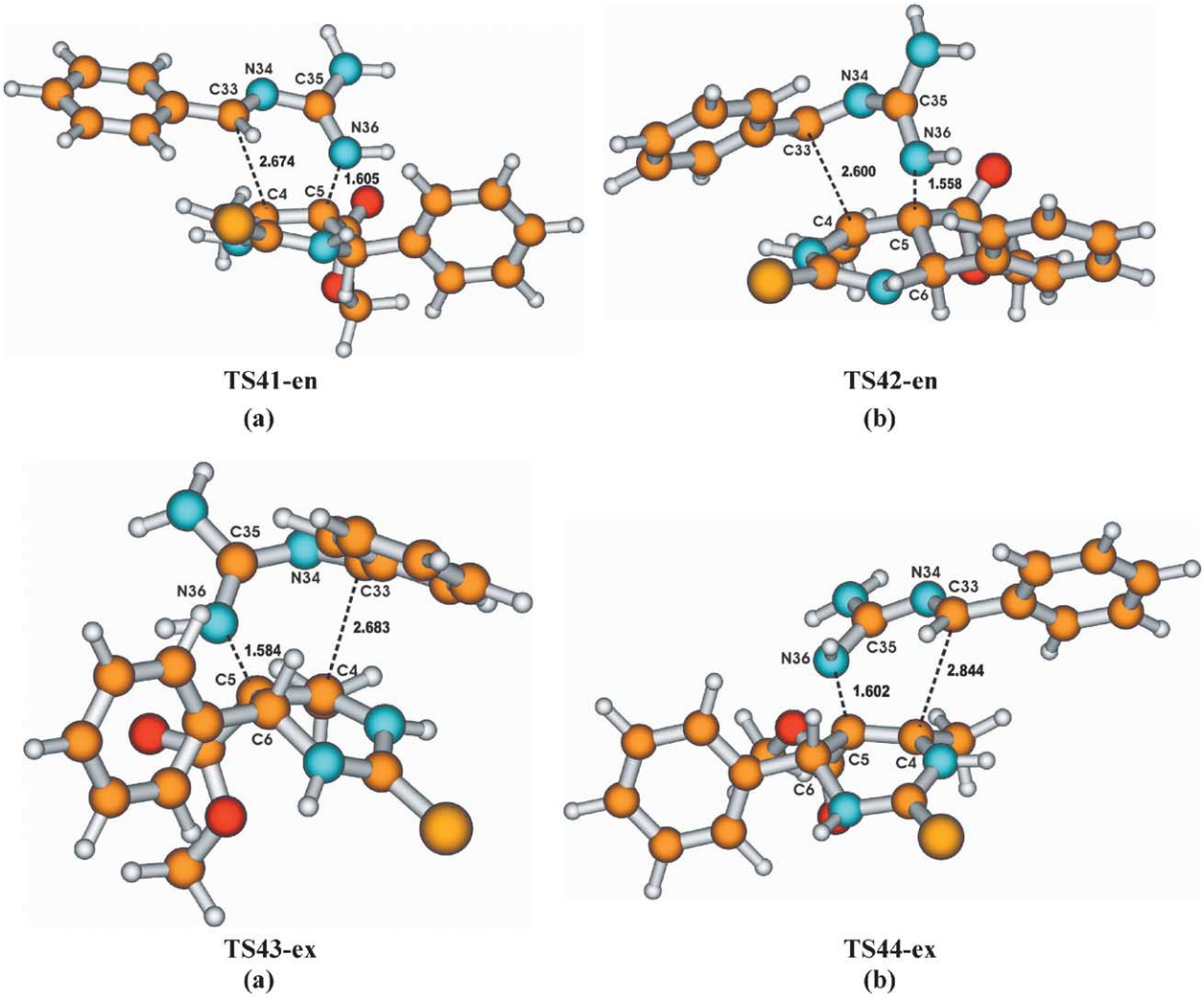


Figure 5. Transition state structures corresponding to regioisomer **2** for the [4+2]cycloaddition reaction between **1** and **4a**. (a) *trans*-approach; (b) *cis*-approach.

Table 2. PM3 relative energies (kcal mol^{-1}) to reactants[a] for the stationary points of the reactions

S. no.	Stationary points	Rel. energies	Stationary points	Rel. energies
1	TS11-en	48.23	P11-en	6.05
2	TS12-en	50.45	P12-en	5.92
3	TS13-ex	49.71	P13-ex	3.79
4	TS14-ex	50.22	P14-ex	2.49
5	TS21-en	60.22	P21-en	4.72
6	TS22-en	65.27	P22-en	0.84
7	TS23-ex	64.35	P23-ex	4.62
8	TS24-ex	57.63	P24-ex	2.29
9	TS31-en	32.91	P31-en	−1.57
10	TS32-en	38.86	P32-en	−2.78
11	TS33-ex	37.36	P33-ex	−1.06
12	TS34-ex	38.03	P34-ex	−6.66
13	TS41-en	37.30	P41-en	−11.62
14	TS42-en	43.23	P42-en	−14.79
15	TS43-ex	46.25	P43-ex	−8.57
16	TS44-ex	49.15	P44-ex	−10.19

[a] PM3 heat of formation (kcal mol^{-1}) for the reactants are: **1**+**2a**=38.80; **1**+**4a**=44.34.

(77.25 kcal mol^{-1}) is 4.45 kcal mol^{-1} lower as compared to the TS33-ex (81.70 kcal mol^{-1}) for the HDA reaction between **1** and **4a**.

Moreover, it has been inferred from the relative energies of stationary points summarized in Table 2 that, though the calculated difference in energies of the alternative products is small, but it is highly significant. Hence, reaction pathway along the *endo* approach experiences the relatively smaller activation barrier (48.23 kcal mol^{-1} and 32.91 kcal mol^{-1} for the formation of **3a** and **5a**, respectively) as compared to the corresponding *exo* approach and thus is the favourable route. The PM3 optimized geometries of **3a** and **5a** is shown in Figure 6. The predicted regiochemistry agrees quite well with the experimental outcome.

We also found that the three-carbon atoms involved in the bond formation are significantly pyramidalized, as it can be seen from the bond angles shown in Table 3, which are in close proximity to the sp^3 geometry. In addition, the carbon atom of the diene **2a**, which is not involved in the bond formation, is slightly pyramidal, with the attached hydrogen (H44) laying 7.3° out of the diene plane. This distortion

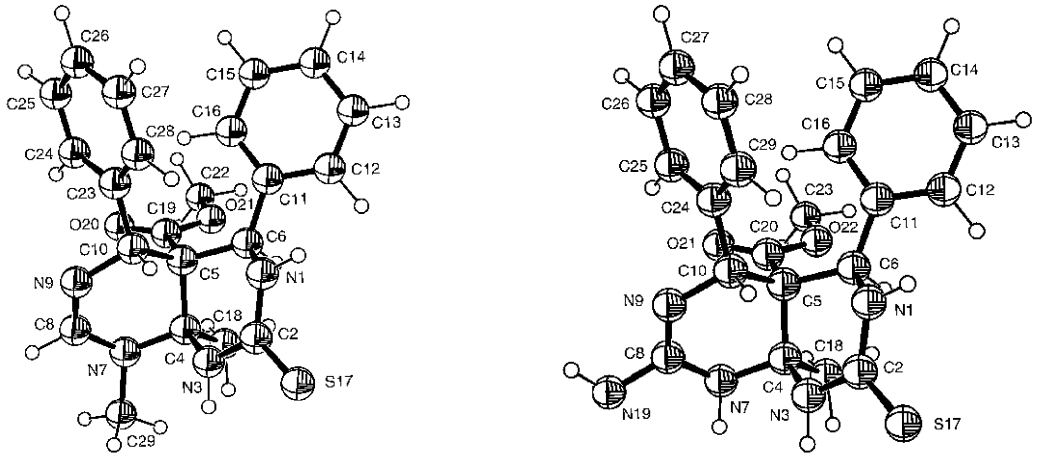


Figure 6. The ORTEP plot of **3a** and **5a** with atom numbering. Thermal ellipsoids are scaled to 50% probability. The atom numbering is arbitrary and has nothing to do with the IUPAC nomenclature.

probably allows for better overlap between the diene π-system and the new forming bonds.

Furthermore, the transition vector (TV),[23] that is, the eigen-vector associated to the unique negative eigen-value of the force constant matrix is dominated by the motion of new forming C–C and C–N bond and the extent of asynchronicity (Δr) can be measured by means of difference between the distances of the bonds that are being formed in the cycloaddition reactions, that is, $\Delta r = d(\text{C36–C5}) - d(\text{N33–C4})$ at different TSs obtained for the studied reactions. The corresponding Δr-values are found in the range of 0.982–0.936 and shown in Table 3 along with selected geometrical parameters for the different TSs.

Likewise, two TSs for diastereomeric reaction between **1** and **4a** with hydrogen at N33 in *syn* and *anti* conformation has been determined. The diastereomeric TSs for the reaction under study differ by the location of nitrogen lone pair. In syn approach the lone pair rotates inward toward the diene fragment, while in anti approach, the lone pair rotates away from the diene fragment. The relief of lone pair-π-electron repulsion in *anti* approach compared to *syn* leads to a shorter N-C4 distance (1.524 Å) at transition state structure (TS31) and consequently results lower energy in the former (32.91 kcal mol^{-1}). The same effect was noticed by the Houk in the Diels–Alder reaction of formaldimine with 1,3-butadiene[24] and Bachrach in DA reaction of 1-aza-1,3-butadiene.[25] This implies that even though two-orbitals on the nitrogen (the π- and the lone pair orbital) can interact with the dienophile; the preferred path rotates the lone pair away from the reaction zone. Only the π-orbital participates in the formation of new C–N bond.

Thus, on the basis of the above rationalization the observed HDA cycloadditions can be predicted as the asynchronous concerted ones, vis-à-vis in good agreement with the experimental evidences.

2.3. Frontier molecular orbital analysis

The reaction studied in this work can also be understood through the frontier molecular orbital (FMO)[26] model based on the energy gap of HOMO and LUMO. The FMO model can be appropriate to explain the observed reaction rate for the cycloaddition reactions of **1** with different dienes, that is,

Table 3. Selected geometrical parameters and asynchronicity (Δr) for the TSs located on cycloaddition reaction profile

	TS11-en	TS13-ex	TS31-en	TS33-ex
C4–N33[a]	1.53	1.59	1.52	1.59
C5–C36[a]	2.51	2.57	2.50	2.53
C4–C5[a]	1.51	1.48	1.51	1.46
N3–C4–N33[b]	101.37	104.06	105.29	099.91
C6–C5–C36[b]	112.68	109.86	114.53	100.50
C5–C4–N33[b]	113.21	111.58	114.097	113.91
N3–C4–N33[b]	101.37	104.06	105.29	99.91
C6–C5–C36[b]	112.68	108.86	114.53	100.50
C4–C5–C36[b]	97.70	96.42	97.03	100.28
C5–C36–N35[b]	93.09	90.91	93.18	93.08
N3–C4–N33–C34[c]	85.84	−146.23	106.71	−114.46
C6–C5–C36–N35[c]	−170.71	051.02	−178.09	060.49
N33–C34–N35–C36[c]	−23.43	−28.37	−16.76	−18.88
Δr	0.982	0.983	0.976	0.936

[a] Distances in Å.
[b] Angles in degrees.
[c] Torsion angles in degrees; $\Delta r = d(\text{C5–C36}) - d(\text{C4–N33})$.

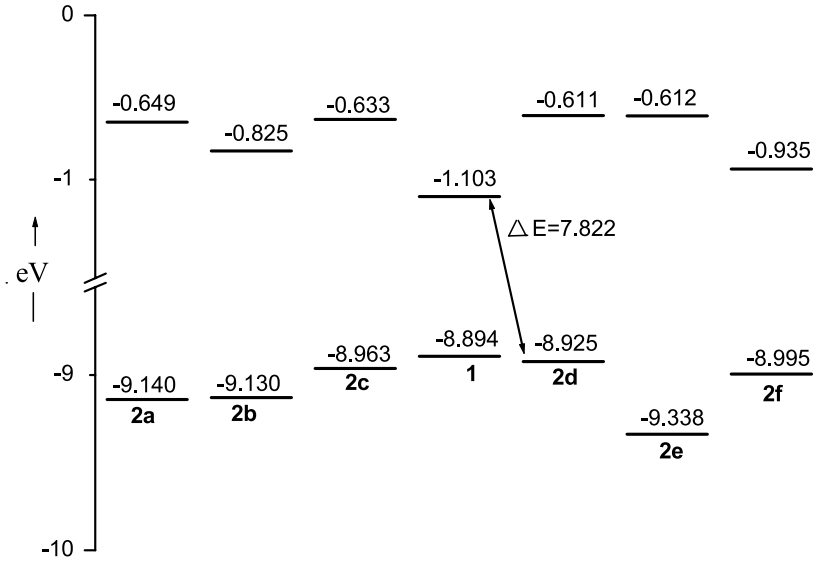


Figure 7. Frontier molecular orbitals of dienophile **1** and dienes **2a–f**.

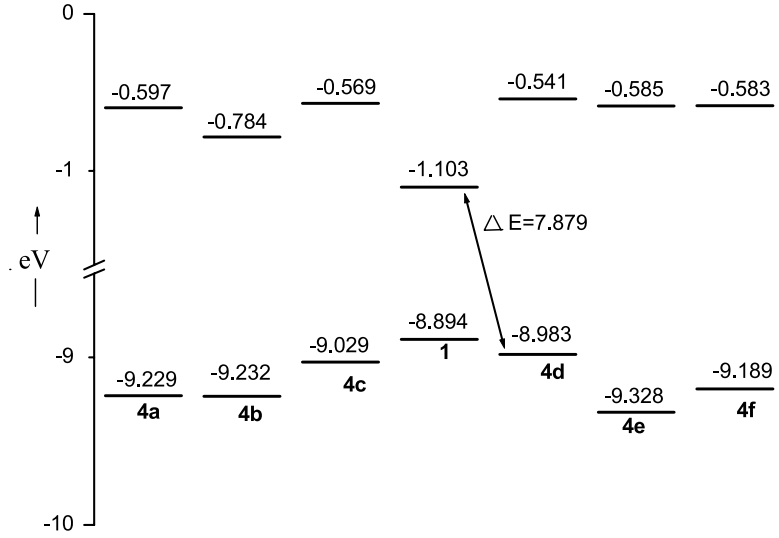


Figure 8. Frontier molecular orbitals of dienophile **1** and dienes **4a–f**.

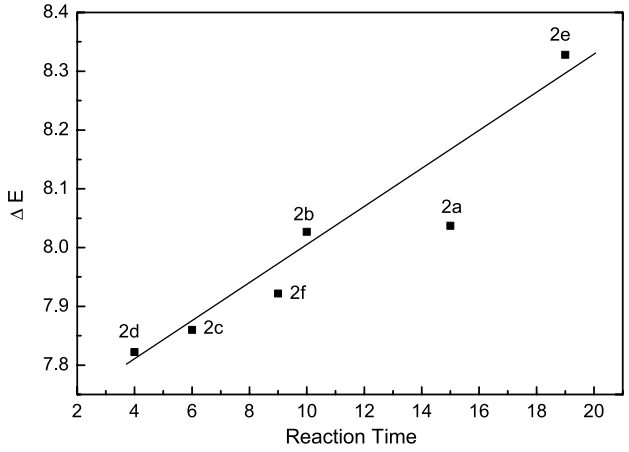


Figure 9. Plot between the reaction time and energy difference of frontier molecular orbital for reaction of **1** and dienes **2a–f** (ΔE=HOMO−LUMO).

2a–f and **4a–f** (Table 1). It has been realized from the Figures 7 and 8 that the observed reactions are E_{HOMO}(diene)−E_{LUMO}(dienophile) controlled, as is the case for normal Diels–Alder cycloaddition (NDAC). An overview of the data presented in Table 1 shows that the reaction between **1** and **2d** occur at much faster rate, which is also supported by the least $HOMO_{diene}-LUMO_{dienophile}$ energy gap in the series as depicted in the Figure 9. However, the insertion of electron donating group such as –OH and –Cl at the 4-phenyl ring of **2** increases the energy gap and subsequently retards the reaction rate (Fig. 9). In general observed reaction rate follows the pattern: **2d**>**2c**>**2f**>**2b**>**2a**>**2e**. Conversely, cycloadditions with the guanidine derivative, that is, unsubstituted *N*-terminal of diene fragment bearing NH_2 at neighbouring carbon atom give rise to lower HOMO as compared to corresponding formamidine derivatives. Hence, the $HOMO_{diene}-LUMO_{dienophile}$ energy gap

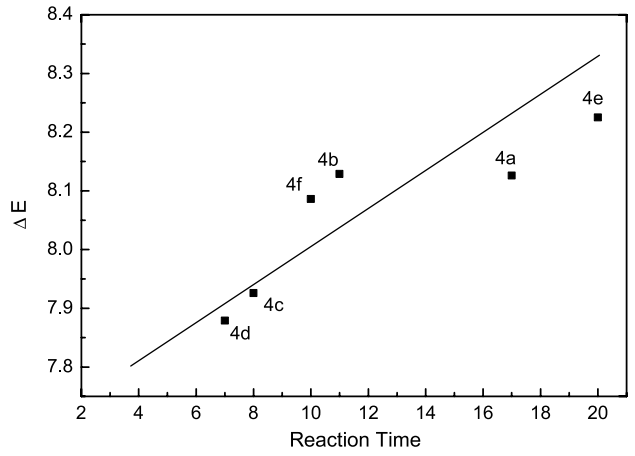


Figure 10. Plot between the reaction time and energy difference of frontier molecular orbital for reaction of **1** and dienes **4a–f** (ΔE=HOMO−LUMO).

increases, which resulted in the increase reaction time (Fig. 10).

3. Conclusion

Present studies demonstrated the HDA reaction as an expeditious and efficient procedure for the synthesis of potent pyrimido[4,5-*d*]pyrimidine conformers bearing different substituents on the C-5 phenyl ring, after successfully exploiting for the first time the dienophilic behaviour of the Biginelli compound.

As per the theoretical calculations, the studied HDA reaction of 4-phenyl-tetrahydropyrimidine-5-carboxylate derivative with substituted methyl formamidine and guanidine can be considered as an asynchronous concerted process.

Semiempirical PM3 studies supported the experimental results, suggesting a preference for the *endo* reaction pathway over the *exo* approach of the dienophile towards the diene fragment to obtain the target compounds owing to lower activation barrier of 48.23 kcal mol^{-1} and 32.91 kcal mol^{-1} for adduct formation (**3a** and **5a**, respectively). The diastereomeric reactions of (*E*)- and (*Z*)-*N*-benzylidine-guanidine displayed lower activation energy, that is, 32.91 kcal mol^{-1} for the former, which is attributed to the build-up of lone pair-π-bond repulsion during the DA reaction of *Z*-isomer. Moreover, FMO analysis reasonably predicts the observed reaction rate for the investigated cycloaddition reactions.

Therefore, normal electron demand hetero Diels–Alder reaction with the unusual dienophile and dienes presented in this work can be translated into a facile route for the construction of structurally diverse novel heterocycles of pharmacological importance, which can be envisaged as new lead compounds. In due course, the biological screening studies of all the synthesized compounds will be the subject of further investigation.

4. Experimental

Melting points (mp) were determined on an electrothermal apparatus by open capillary method and are uncorrected. All the chemicals used were of AR grade purity from E Merck. Solvents were freshly distilled and dried prior to use. IR spectra were recorded as KBr pellets on a Shimadzu 460 FTIR-spectrometer. Frequencies are reported in cm^{-1}. The NMR spectra were recorded on a Jeol NMR 200 MHz (^1H) and Bruker DRX 400 MHz (^{13}C) spectrometers in $CDCl_3$. Chemical shifts (δ) are reported in ppm value relative to tetramethylsilane (TMS) and coupling constants (*J*) in Hz. Mass spectra were taken with a Jeol D-300 spectrometer. Purity of all the synthesized compounds were ascertained by TLC resolution studies on silica gel G (E Merck) using ethyl acetate–xylene (4:6, v/v) as eluent and HPLC analysis, performed on Shimadzu LC10AS using L7 phenyl packing column, a 254 nm UV Shimadzu ASVP detector and acetonitrile/methanol/water (60:30:10) as eluent with a flow rate of 1 ml/min. Compounds **1**,[27] **2a–f** [28] and **4a–f**[28] were synthesized by modified literature method.

4.1. General procedure for the synthesis of 5-aryl-8,8a-dimethyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido[4,5-*d*]pyrimidine-4a-carboxylic acid methyl ester (3a–f)

To a solution of 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylic acid methyl ester **1** (6.1 g, 10 mmol) in anhydrous toluene (15 ml), was added substituted *N*-arylidene-*N*′-methyl-formamidine **2a–f** (20 mmol) at room temperature and the mixture was allowed to reflux or stirring for the required time (see Table 1). After the completion of reaction, the solvent was distilled off under reduced pressure and the residue was recrystallized from chloroform:petroleum ether (1:2) affording the corresponding pyrimido[4,5-*d*]pyrimidines in good to excellent yields.

4.1.1. 5-Phenyl-8,8a-dimethyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido[4,5-*d*]pyrimidine-4a-carboxylic acid methyl ester (3a). Mp (°C) 154–156. White solid. Anal. Calcd for $C_{22}H_{24}N_4O_2S$ (408.52): C, 64.68; H, 5.92; N, 13.71. Found: C, 64.60; H, 5.85, N, 13.65. IR (KBr) (ν, cm^{-1}) 3216 (NH), 3012 (CH sp^2), 2850 (CH sp^3), 1750 (C=O, ester), 1595 (C=C/C=N), 1530, 1473, 1400 (C⎓C ring str.), 1302 (C–N), 1070 (C=S); ^1H NMR (δ ppm) 2.42 (s, 3H, CH_3) 2.52 (s, 3H, N–CH_3), 3.71 (s, 3H, $COOCH_3$) 4.93 (d, 1H, CH, $^4J_{HH}$=1.1 Hz), 5.2 (dd, 1H, CH, $^3J_{HH}$=3.0 Hz, $^4J_{HH}$=1.3 Hz), 7.1 (s, 10H, 2×C_6H_5), 7.75 (br s, 1H, NH), 8.2 (s, 1H, N=CH), 9.15 (d, 1H, NH, $^3J_{HH}$=3.4 Hz); ^{13}C NMR (δ ppm) 183.6 (C=S), 174.4 (C=O), 145.5 (C=N), 141.4, 139.4, 132.6, 129.5, 129.4, 125.4, 123.6, 123.0 (2×Ph), 76.1 (C_{4a}), 74.0 (C_{8a}), 51.5 (C_4), 51.0 (CH_3, ester), 45.9 (C_5), 28.7 (N–CH_3) 20.8 (CH_3); FAB-MS *m*/*z* (RA %) 408 (M^+, 12).

4.1.2. 5-(4-Chlorophenyl)-8,8a-dimethyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido[4,5-*d*]pyrimidine-4a-carboxylic acid methyl ester (3b). Mp (°C) 152–154. White solid. Anal. Calcd for $C_{22}H_{23}ClN_4O_2S$ (442.96): C, 59.65; H, 5.23; N, 12.65. Found: C, 59.58; H, 5.17; N, 12.57. IR (KBr) (ν, cm^{-1}) 3219 (NH), 3010 (CH

sp^2), 2860 (CH sp^3), 1752 (C=O, ester), 1592 (C=C/C=N), 1523, 1470, 1410 (C⋯C ring str.), 1307 (C–N), 1050 (C=S), 585 (C-Cl); ^{1}H NMR (δ ppm) 2.47 (s, 3H, CH_3) 2.51 (s, 3H, N–CH_3), 3.79 (s, 3H, $COOCH_3$) 4.89 (d, 1H, CH, $^4J_{HH}$=1.1 Hz), 5.1 (dd, 1H, CH, $^3J_{HH}$=3.0 Hz, $^4J_{HH}$=1.3 Hz), 7.0 (s, 5H, C_6H_5), 7.21 (d, 2H, Ar-H, $^3J_{HH}$=8.0 Hz), 7.65 (br s, 1H, NH), 7.82 (d, 2H, Ar-H, $^3J_{HH}$=6.0 Hz), 8.1 (s, 1H, N=CH), 9.19 (d, 1H, NH, $^3J_{HH}$=3.4 Hz); ^{13}C NMR (δ ppm) 184.8 (C=S), 174.1 (C=O), 144.2 (C=N), 142.1, 139.2, 131.7, 129.4, 129.3, 128.6, 128.4, 121.3 (Ph/Ar), 77.1 (C_{4a}), 72.8 (C_{8a}), 51.2 (C_4), 49.7 (CH_3, ester), 45.7 (C_5), 28.1 (N–CH_3) 20.7 (CH_3); FAB-MS *m/z* (RA %) 443 (M^+, 15), 445 (M^++2, 5).

4.1.3. 5-(4-Hydroxyphenyl)-8,8a-dimethyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido[4,5-*d*]pyrimidine-4a-carboxylic acid methyl ester (3c). Mp (°C) 157–159. Reddish solid. Anal. Calcd for $C_{22}H_{24}N_4O_3S$ (424.51): C, 62.24; H, 5.70; N, 13.20. Found: C, 62.18; H, 5.62; N, 13.12. IR (KBr) (ν, cm^{-1}) 3560 (OH), 3234 (NH), 3017 (CH sp^2), 2857 (CH sp^3), 1750 (C=O, ester), 1590 (C=C/C=N), 1522, 1475, 1402 (C⋯C ring str.), 1305 (C–N), 1060 (C=S); ^{1}H NMR (δ ppm) 2.42 (s, 3H, CH_3), 2.54 (s, 3H, N–CH_3), 3.72 (s, 3H, $COOCH_3$), 4.84 (d, 1H, CH, $^4J_{HH}$=1.1 Hz), 5.3 (dd, 1H, CH, $^3J_{HH}$=3.0 Hz, $^4J_{HH}$=1.3 Hz), 7.0 (s, 5H, C_6H_5), 7.24 (d, 2H, Ar-H, $^3J_{HH}$=8.0 Hz), 7.62 (br s, 1H, NH), 7.81 (d, 2H, Ar-H, $^3J_{HH}$=6.0 Hz), 8.2 (s, 1H, N=CH), 9.12 (d, 1H, NH, $^3J_{HH}$=3.4 Hz), 10.2 (br s, 1H, OH); ^{13}C NMR (δ ppm) 185.2 (C=S), 175.2 (C=O), 145.5 (C=N), 141.1, 139.4, 132.0, 129.4, 129.1, 128.9, 128.7, 115.2 (Ph, Ar), 76.6 (C_{4a}), 73.5 (C_{8a}), 53.4 (C_4), 51.2 (CH_3, ester), 46.1 (C_5), 28.7 (N–CH_3) 20.9 (CH_3), FAB-MS *m/z* (RA %) 424 (M^+, 18).

4.1.4. 5-(4-Methoxyphenyl)-8,8a-dimethyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido[4,5-*d*]pyrimidine-4a-carboxylic acid methyl ester (3d). Mp (°C) 161–163. Yellow-brown solid. Anal. Calcd for $C_{23}H_{26}N_5O_3S$ (438.54): C, 62.99; H, 5.98; N, 12.78. Found: C, 62.92; H, 5.91; N, 12.70. IR (KBr) (ν, cm^{-1}) 3220 (NH), 3015 (CH sp^2), 2850 (CH sp^3), 1760 (C=O, ester), 1600 (C=C/C=N), 1550, 1440, 1410 (C⋯C ring str.), 1300 (C–N), 1072 (C=S); ^{1}H NMR (δ ppm) 2.45 (s, 3H, CH_3), 2.51 (s, 3H, N–CH_3), 3.4 (s, 3H, OCH_3), 3.82 (s, 3H, $COOCH_3$), 4.97 (d, 1H, CH, $^4J_{HH}$=1.1 Hz), 5.1 (dd, 1H, CH, $^3J_{HH}$=3.0 Hz, $^4J_{HH}$=1.3 Hz), 7.1 (s, 5H, C_6H_5), 7.22 (d, 2H, Ar-H, $^3J_{HH}$=8.0 Hz), 7.64 (br s, 1H, NH), 7.83 (d, 2H, Ar-H, $^3J_{HH}$=6.0 Hz), 8.1 (s, 1H, N=CH), 9.14 (d, 1H, NH, $^3J_{HH}$=3.4 Hz); ^{13}C NMR (δ ppm) 183.4 (C=S), 174.1 (C=O), 150.5 (C=N), 146.4, 137.5, 132.1, 128.4, 128.3, 120.6, 120.4, 113.4 (Ph/Ar), 76.1 (C_{4a}), 74.4 (C_{8a}), 56.0 (OCH_3), 51.5 (C_4), 51.0 (CH_3, ester), 45.9 (C_5), 28.6 (N–CH_3) 21.4 (CH_3); FAB-MS *m/z* (RA %) 438 (M^+, 13).

4.1.5. 5-(4-Ethylphenyl)-8,8a-dimethyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido[4,5-*d*]pyrimidine-4a-carboxylic acid methyl ester (3e). Mp (°C) 153–155. Yellow solid. Anal. Calcd for $C_{24}H_{28}N_4O_2S$ (436.57): C, 66.03; H, 6.46; N, 12.83. Found: C, 62.98; H, 6.40; N, 12.76. IR (KBr) (ν, cm^{-1}) 3210 (NH), 3015 (CH sp^2), 2862 (CH sp^3), 1750 (C=O, ester), 1595 (C=C/C=N), 1500, 1472, 1400 (C⋯C ring str.), 1306 (C–N), 1050 (C=S), 722 (CH_2); ^{1}H NMR (δ ppm) 0.9 (t, 3H, CH_3, $^3J_{HH}$=8.0 Hz), 2.41 (s, 3H, CH_3), 2.52 (s, 3H, N–CH_3), 3.74 (s, 3H, $COOCH_3$), 4.35 (q, 2H, CH_2, $^3J_{HH}$=8.0 Hz), 4.92 (d, 1H, CH, $^4J_{HH}$=1.1 Hz), 5.22 (dd, 1H, CH, $^3J_{HH}$=3.0 Hz, $^4J_{HH}$=1.3 Hz), 7.0 (s, 5H, C_6H_5), 7.21 (d, 2H, Ar-H, $^3J_{HH}$=8.0 Hz), 7.62 (br s, 1H, NH), 7.84 (d, 2H, Ar-H, $^3J_{HH}$=6.0 Hz), 8.2 (s, 1H, N=CH), 9.21 (d, 1H, NH, $^3J_{HH}$=3.4 Hz); ^{13}C NMR (δ ppm) 184.7 (C=S), 174.3 (C=O), 145.5 (C=N), 139.4, 137.2, 136.4, 128.3, 127.5, 127.1, 126.4, 125.5 (Ph/Ar), 76.6 (C_{4a}), 72.7 (C_{8a}), 49.3 (C_4), 48.6 (CH_3, ester), 45.9 (C_5), 28.9 (N–CH_3), 28.6 (CH_2) 20.8 (CH_3), 16.1 (CH_3); FAB-MS *m/z* (RA %) 436 (M^+, 15).

4.1.6. 5-(4-Methylphenyl)-8,8a-dimethyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido[4,5-*d*]pyrimidine-4a-carboxylic acid methyl ester (3f). Mp (°C) 151–153. Pale yellow solid. Anal. Calcd for $C_{23}H_{26}N_4O_2S$ (422.54): C, 65.38; H, 6.20; N, 13.26. Found: C, 65.31; H, 6.13; N, 13.20. IR (KBr) (ν, cm^{-1}) 3240 (NH), 3010 (CH sp^2), 2855 (CH sp^3), 1758 (C=O, ester), 1592 (C=C/C=N), 1540, 1434, 1410 (C⋯C ring str.), 1310 (C–N), 1054 (C=S); ^{1}H NMR (δ ppm) 2.38 (s, 3H, CH_3), 2.45 (s, 3H, CH_3) 2.54 (s, 3H, N–CH_3), 3.81 (s, 3H, $COOCH_3$) 4.94 (d, 1H, CH, $^4J_{HH}$=1.1 Hz), 5.2 (dd, 1H, CH, $^3J_{HH}$=3.0 Hz, $^4J_{HH}$=1.3 Hz), 7.0 (s, 10H, C_6H_5), 7.24 (d, 2H, Ar-H, $^3J_{HH}$=8.0 Hz), 7.64 (br s, 1H, NH), 7.81 (d, 2H, Ar-H, $^3J_{HH}$=6.0 Hz), 8.1 (s, 1H, N=CH), 9.12 (d, 1H, NH, $^3J_{HH}$=3.4 Hz); ^{13}C NMR (δ ppm) 184.3 (C=S), 176.4 (C=O), 140.4 (C=N), 139.6, 136.4, 134.9, 129.2, 129.1, 128.7, 128.4, 119.6 (Ph/Ar), 76.7 (C_{4a}), 72.9 (C_{8a}), 51.2 (C_4), 49.4 (CH_3, ester), 46.2 (C_5), 28.7 (N–CH_3), 21.8 (CH_3), 20.7 (CH_3); FAB-MS *m/z* (RA %) 422 (M^+, 14).

4.2. General procedure for the synthesis of 7-amino-5-aryl-8a-methyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido[4,5-*d*]pyrimidine-4a-carboxylic acid methyl ester (5a–f)

To a solution of 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylic acid methyl ester **1** (6.1 g, 10 mmol) in anhydrous toluene (15 ml), was added substituted *N*-arylidene-guanidine **4a–f** (20 mmol) at room temperature and the mixture was allowed to reflux or stirring for the required time (see Table 1). After the completion of reaction, the solvent was distilled off under reduced pressure and the residue was recrystallized from chloroform:petroleum ether (1:2) affording the corresponding desired pyrimido[4,5-*d*]pyrimidines in good to excellent yields.

4.2.1. 7-Amino-5-phenyl-8a-methyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido[4,5-*d*]pyrimidine-4a-carboxylic acid methyl ester (5a). Mp (°C) 148–150. White solid. Anal. Calcd for $C_{21}H_{23}N_5O_2S$ (409.51): C, 61.59; H, 5.66; N, 17.10. Found: C, 61.52; H, 5.60; N, 17.02. IR (KBr) (ν, cm^{-1}) 3410 (NH_2-sym), 3365 (NH_2-asy), 3216 (NH), 2900 (CH sp^3), 1760 (C=O, ester), 1590 (C=C/C=N), 1522, 475, 1401 (C⋯C ring str.), 1312 (C–N), 1053 (C=S); ^{1}H NMR (δ ppm) 2.41 (s, 3H, CH_3), 3.81 (s, 3H, $COOCH_3$), 4.91 (d, 1H, CH, $^4J_{HH}$=1.4 Hz), 5.3 (dd, 1H, CH, $^3J_{HH}$=3.0 Hz, $^4J_{HH}$=1.3 Hz), 6.0 (s, 2H, NH_2), 7.0 (s, 10H, 2×C_6H_5), 7.7 (br s, 1H, NH), 9.2 (br s, 1H, NH), 10.12 (d, 1H, NH, $^3J_{HH}$=3.4 Hz); ^{13}C NMR (δ ppm) ^{13}C NMR (δ

ppm) 183.8 (C=S), 176.1 (C=O), 145.3 (C=N), 141.2, 139.2, 129.8, 129.6, 127.4, 127.1, 124.6, 123.9 (2×Ph), 78.6 (C_{4a}), 61.5 (C_{8a}), 51.2 (C_4), 51.0 (CH_3, ester), 42.5 (C_5), 20.8 (CH_3); FAB-MS *m/z* (RA %) 409 (M^+, 15).

4.2.2. 7-Amino-5-(4-chlorophenyl)-8a-methyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido[4,5-*d*]-pyrimidine-4a-carboxylic acid methyl ester (5b). Mp (°C) 144–146. White solid. Anal. Calcd for $C_{21}H_{22}ClN_5O_2S$ (443.95): C, 56.81; H, 4.99; N, 15.78. Found: C, 56.74; H, 4.92; N, 15.71. IR (KBr) (ν, cm^{-1}) 3420 (NH_2-sym), 3361 (NH_2-asy), 3215 (NH), 2865 (CH sp^3), 1752 (C=O, ester), 1595 (C=C/C=N), 1534, 1481, 1407 (C⎓C ring str.), 1302 (C–N), 1062 (C=S), 580 (C-Cl); ^{1}H NMR (δ ppm) 2.44 (s, 3H, CH_3), 3.83 (s, 3H, $COOCH_3$), 4.95 (d, 1H, CH, $^4J_{HH}$= 1.4 Hz), 5.3 (dd, 1H, CH, $^3J_{HH}$=3.0 Hz, $^4J_{HH}$=1.3 Hz), 6.1 (s, 2H, NH_2), 7.0 (s, 5H, C_6H_5), 7.22 (d, 2H, Ar-H, $^3J_{HH}$=8.0 Hz), 7.65 (br s, 1H, NH), 7.83 (d, 2H, Ar-H, $^3J_{HH}$=6.0 Hz), 9.0 (br s, 1H, NH), 10.14 (d, 1H, NH, $^3J_{HH}$=3.4 Hz); ^{13}C NMR (δ ppm) 185.0 (C=S), 177.2 (C=O), 142.8 (C=N), 139.4, 137.2, 131.2, 129.2, 129.2, 127.6, 127.2, 125.6 (Ph/Ar), 78.3 (C_{4a}), 61.7 (C_{8a}), 52.1 (C_4), 51.2 (CH_3, ester), 43.6 (C_5), 24.2 (CH_3); FAB-MS *m/z* (RA %) 444 (M^+, 12), 446 (M^++2, 4).

4.2.3. 7-Amino-5-(4-hydroxyphenyl)-8a-methyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido-[4,5-*d*]pyrimidine-4a-carboxylic acid methyl ester (5c). Mp (°C) 148–150. Reddish solid. Anal. Calcd for $C_{21}H_{23}N_5O_3S$ (425.51): C, 59.28; H, 5.45; N, 16.46. Found: C, 59.23; H, 5.38; N, 16.39. IR (KBr) (ν, cm^{-1}) 3492 (OH), 3425 (NH_2-sym), 3367 (NH_2-asy), 3210 (NH), 2870 (CH sp^3), 1760 (C=O, ester), 1592 (C=C/C=N), 1534, 1451, 1425 (C⎓C ring str.), 1306 (C–N), 1060 (C=S); ^{1}H NMR (δ ppm) 2.42 (s, 3H, CH_3), 3.82 (s, 3H, $COOCH_3$), 4.91 (d, 1H, CH, $^4J_{HH}$=1.4 Hz), 5.3 (dd, 1H, CH, $^3J_{HH}$=3.0 Hz, $^4J_{HH}$=1.3 Hz), 6.12 (s, 2H, NH_2), 7.0 (s, 5H, C_6H_5), 7.26 (d, 2H, Ar-H, $^3J_{HH}$=8.0 Hz), 7.61 (br s, 1H, NH), 7.8 (d, 2H, Ar-H, $^3J_{HH}$=6.0 Hz), 9.1 (br s, 1H, NH), 10.18 (d, 1H, NH, $^3J_{HH}$=3.4 Hz), 12.45 (s, 1H, OH); ^{13}C NMR (δ ppm) 183.7 (C=S), 175.1 (C=O), 146.8 (C=N), 145.1, 139.2, 132.0, 129.7, 129.5, 128.7, 126.1, 115.3 (Ph/Ar), 78.7 (C_{4a}), 62.3 (C_{8a}), 51.5 (C_4), 51.0 (CH_3, ester), 42.8 (C_5), 23.3 (CH_3); FAB-MS *m/z* (RA %) 425 (M^+, 16).

4.2.4. 7-Amino-5-(4-methoxyphenyl)-8a-methyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido-[4,5-*d*]pyrimidine-4a-carboxylic acid methyl ester (5d). Mp (°C) 143–145. Yellow-brown solid. Anal. Calcd for $C_{22}H_{25}N_5O_3S$ (439.53): C, 60.12; H, 5.73; N, 15.93. Found: C, 60.04; H, 5.67; N, 15.87. IR (KBr) (ν, cm^{-1}) 3415 (NH_2-sym), 3305 (NH_2-asy), 3215 (NH), 2875 (CH sp^3), 1752 (C=O, ester), 1590 (C=C/C=N), 1561, 1470, 1401 (C⎓C ring str.), 1305 (C–N), 1057 (C=S); ^{1}H NMR (δ ppm) 2.48 (s, 3H, CH_3), 3.4 (s, 3H, OCH_3), 3.86 (s, 3H, $COOCH_3$), 4.92 (d, 1H, CH, $^4J_{HH}$=1.4 Hz), 5.1 (dd, 1H, CH, $^3J_{HH}$= 3.0 Hz, $^4J_{HH}$=1.3 Hz), 6.17 (s, 2H, NH_2), 7.1 (s, 5H, C_6H_5), 7.28 (d, 2H, Ar-H, $^3J_{HH}$=8.0 Hz), 7.67 (br s, 1H, NH), 7.82 (d, 2H, Ar-H, $^3J_{HH}$=6.0 Hz), 9.3 (br s, 1H, NH), 10.21 (d, 1H, NH, $^3J_{HH}$=3.4 Hz), ^{13}C NMR (δ ppm) 184.2 (C=S), 178.4 (C=O), 145.8 (C=N), 143.1, 139.6, 134.5, 129.4, 129.1, 126.6, 126.2, 117.9 (Ph/Ar), 77.8 (C_{4a}), 61.1 (C_{8a}), 56.1 (OCH_3), 52.7 (C_4), 51.2 (CH_3, ester), 42.7 (C_5), 23.1 (CH_3); FAB-MS *m/z* (RA %) 439 (M^+, 10).

4.2.5. 7-Amino-5-(4-ethylphenyl)-8a-methyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido[4,5-*d*]pyrimidine-4a-carboxylic acid methyl ester (5e). Mp (°C) 141–143. Yellow solid. Anal. Calcd for $C_{23}H_{27}N_5O_2S$ (437.56): C, 63.13; H, 6.22; N, 16.01. Found: C, 63.06; H, 6.14; N, 15.93. IR (KBr) (ν, cm^{-1}) 3425 (NH_2-sym), 3310 (NH_2-asy), 3217 (NH), 2869 (CH sp^3), 1757 (C=O, ester), 1600 (C=C/C=N), 1507, 1480, 1400 (C⎓C ring str.), 1310 (C–N), 1050 (C=S), 725 (CH_2); ^{1}H NMR (δ ppm) 0.9 (t, 3H, CH_3, $^3J_{HH}$=8.0 Hz), 2.43 (s, 3H, CH_3), 3.87 (s, 3H, $COOCH_3$), 4.45 (q, 2H, CH_2, $^3J_{HH}$=8.0 Hz), 4.74 (d, 1H, CH, $^4J_{HH}$=1.4 Hz), 5.12 (dd, 1H, CH, $^3J_{HH}$=3.0 Hz, $^4J_{HH}$=1.3 Hz), 6.22 (s, 2H, NH_2), 7.0 (s, 5H, C_6H_5), 7.26 (d, 2H, Ar-H, $^3J_{HH}$=8.0 Hz), 7.65 (br s, 1H, NH), 7.84 (d, 2H, Ar-H, $^3J_{HH}$=6.0 Hz), 9.2 (br s, 1H, NH), 10.17 (d, 1H, NH, $^3J_{HH}$=3.4 Hz); ^{13}C NMR (δ ppm) 185.1 (C=S), 176.4 (C=O), 141.1 (C=N), 139.6, 137.2, 136.6, 128.5, 128.3 127.7, 126.2, 125.8 (Ph/Ar), 78.5 (C_{4a}), 61.7 (C_{8a}), 51.9 (C_4), 51.0 (CH_3, ester), 42.6 (C_5), 28.4 (CH_2), 24.2 (CH_3), 16.1 (CH_3); FAB-MS *m/z* (RA %) 437 (M^+, 13).

4.2.6. 7-Amino-5-(4-methylphenyl)-8a-methyl-4-phenyl-2-thioxo-1,3,4,5,8,8a-hexahydro-2*H*-pyrimido[4,5-*d*]-pyrimidine-4a-carboxylic acid methyl ester (5f). Mp (°C) 146–148. Pale yellow solid. Anal. Calcd for $C_{22}H_{25}N_5O_2S$ (423.53): C, 62.39; H, 5.95; N, 16.54. Found: C, 62.32; H, 5.88; N, 16.48. IR (KBr) (ν, cm^{-1}) 3417 (NH_2-sym), 3347 (NH_2-asy), 3215 (NH), 2872 (CH sp^3), 1760 (C=O, ester), 1585 (C=C/C=N), 1572, 1453, 1408 (C⎓C ring str.), 1300 (C–N), 1048 (C=S); ^{1}H NMR (δ ppm) 2.37 (s, 3 h, CH_3), 2.41 (s, 3H, CH_3), 3.84 (s, 3H, $COOCH_3$), 4.86 (d, 1H, CH, $^4J_{HH}$=1.4 Hz), 5.23 (dd, 1H, CH, $^3J_{HH}$=3.0 Hz, $^4J_{HH}$= 1.3 Hz), 6.28 (s, 2H, NH_2), 7.0 (s, 5H, C_6H_5), 7.23 (d, 2H, Ar-H, $^3J_{HH}$=8.0 Hz), 7.61 (br s, 1H, NH), 7.84 (d, 2H, Ar-H, $^3J_{HH}$=6.0 Hz), 9.3 (br s, 1H, NH), 10.46 (d, 1H, NH, $^3J_{HH}$=3.4 Hz); ^{13}C NMR (δ ppm) 183.7 (C=S), 178.1 (C=O), 142.3 (C=N), 139.4, 137.9, 135.7, 129.7, 129.1, 128.4, 127.5, 125.6 (Ph/Ar), 78.2 (C_{4a}), 62.3 (C_{8a}), 51.7 (C_4), 51.2 (CH_3, ester), 43.1 (C_5), 23.3 (CH_3), 20.9 (CH_3); FAB-MS *m/z* (RA %) 423 (M^+, 16).

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Synthesis and microbial transformation of β-amino nitriles

Margit Winkler,[a] Ludmila Martínková,[b] Astrid C. Knall,[a] Stefan Krahulec[a] and Norbert Klempier[a,*]

[a]*Institute of Organic Chemistry, Graz University of Technology, Stremayrgasse 16, A-8010 Graz, Austria*
[b]*Institute of Microbiology, Academy of Sciences of the Czech Republic, Videnska 1083, CZ 142 20 Prague 4, Czech Republic*

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Abstract—*Rhodococcus equi* A4, *Rhodococcus erythropolis* NCIMB 11540 and *Rhodococcus* sp. R312 were investigated towards their ability to produce β-amino amides and acids from β-amino nitriles. The microorganisms show comparable trends: five-membered alicyclic 2-amino nitriles were transformed significantly faster than the six-membered compounds and the products of *trans*-2-amino nitriles (amides and acids) were formed considerably faster than the *cis*-counterparts (amides). The *trans*-five membered nitriles gave the amides (**1b**, **5b**) in excellent enantiomeric excess (94–99%), the biotransformation of *trans*-six membered substrates resulted in the formation of the acid (**3c**, **7c**) in excellent ee (87–99%). The ee's of the *cis*-compounds were throughout lower. Fifteen new substances were synthesized and characterized in the course of this work.

1. Introduction

β-Amino acids are key structural components of a variety of natural products and drugs.[1,2] Recently, alicyclic β-amino acids, for example, *trans*-aminocyclopentane carboxylic acid, have been used for the synthesis of β-oligopeptides. The folding properties of such synthetic oligomers with unnatural backbones into defined three-dimensional structures have been explored.[3–5] On the other hand (1*R*,2*S*)-*cis*-aminocyclopentane carboxylic acid (cispentacin) itself is a strong antifungal antibiotic,[6] other alicyclic amino acids can be used in heterocyclic chemistry.[7] This interest in β-amino acids and their synthesis is reflected in several recent reviews.[1,2,8]

In recent years, enzymatic methods have been established as an alternative to the harsh reaction conditions of chemical hydrolysis of nitriles.[9] The respective biocatalysts—nitrilases,[10] nitrile hydratases[11] and amidases—are frequently used as whole cell systems or, less frequently, in purified form by several groups.

In this paper, we report the preparation of β-amino amides and carboxylic acids by whole cells of *Rhodococcus equi* A4, *Rhodococcus* sp. R312 and *Rhodococcus erythropolis* NCIMB 11540. These strains express nitrile hydratase and amidase activity.

2. Results and discussion

In previously published work, we have demonstrated that β-amino nitriles are readily converted to β-amino amides and acids by nitrile hydratase/amidase containing microorganisms.[12,13] In this work, we wish to report on the stereoselective transformation of *cis*- and *trans*-aminocyclopentane-/hexane nitriles (**1a**–**8a** depicted in Fig. 1) in dependence on ring size and relative configuration of the

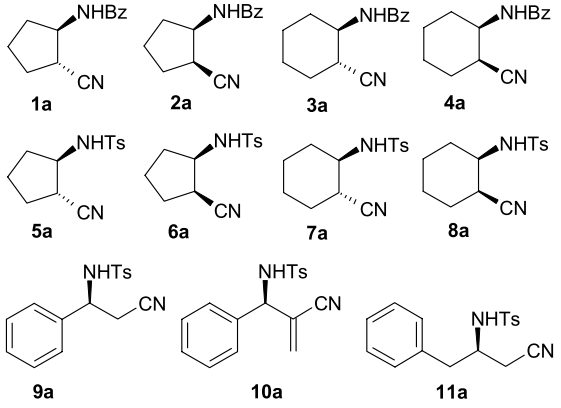

Figure 1. Structures of racemic β-amino nitriles for whole cell transformations (only one enantiomer is depicted).

Keywords: Microbial nitrile hydrolysis; Enantioselectivity; β-Amino acids.
* Corresponding author. Tel.: +43 316 873 8245; fax: +43 316 873 8740; e-mail: klempier@orgc.tu-graz.ac.at

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Table 1. Biotransformations of racemic *N*-protected β-amino nitriles by whole cells—screening

Entry	Substrate	*R. equi* A4[a]			*R. erythropolis* NCIMB 11540[b]			*R.* sp. R 312[c]		
		Nitrile (%)	Amide (%)	Acid (%)	Nitrile (%)	Amide (%)	Acid (%)	Nitrile (%)	Amide (%)	Acid (%)
1	**1a**	0	22	78	0	12	88	0	10	90
2	**2a**	97[d]	3[d]	0[d]	93	4	3	93	3	3
3	**3a**	31	20	50	36	12	52	32	14	54
4	**4a**	99[d]	1[d]	0[d]	91	9	0	94	6	0
5	**5a**	0	13	87	1	1	98	0	0	100
6	**6a**	0	76	24	1	70	29	17	46	37
7	**7a**	0	55	45	2	2	96	2	18	80
8	**8a**	3	96	1	2	92	7	1	90	8
9	**9a**	52	38	9	45	39	16	54	22	24
10	**10a**	6	94	0	2	98	0	6	94	0
11	**11a**	67	18	15	53	26	21	49	21	30

[a] Cell preparation OD 52.
[b] Cell preparation OD 68.
[c] Cell preparation OD 77.
[d] Cell preparation OD 12.

1,2-positions. The acyclic nitriles **9a**–**11a** serve as precursors for β-phenylalanine, α-methylene-β-amino acids and β-homo-phenylalanine, respectively, (Fig. 1).

2.1. Biotransformation

Initial screening experiments were performed using *Rhodococcus equi* A4, *Rhodococcus erythropolis* NCIMB 11540 and *Rhodococcus* sp. R312. Different from our previous work, the microorganisms were cultivated in an inductive medium yielding less biomass, yet with better activity. The results of these screening experiments are depicted in Table 1. In summary they suggest the following general trends: (i) the conversions by the microorganisms with respect to a single substrate structure are comparable. No significant differences in product formation were observed; (ii) the biotransformations of *trans*-compounds are in all cases faster than those of their *cis*-counterparts. The *cis*-benzoates **2a** and **4a** are not accepted as substrates, in contrast, *trans*-**1a** and *trans*-**3a** show rapid conversion; (iii) the conversion of tosylated substrate **6a** is resulting in a significant accumulation of the amide **6b**, while nitrile **5a** is converted to the acid **5c** without accumulating detectable amounts of amide; (iv) the transformation of five-membered alicycles is significantly faster than for the six-membered compounds.

Similar trends, that is, the faster conversion of *trans*-substrates compared to the *cis*-counterparts and the distinct influence of the ring-size on the transformation have been observed for the analogous β-hydroxy cyclopentane/hexane carbonitriles. This was previously reported for *R. equi* A4.[14]

As described later in this paper, the chemical route to the single *cis*-diastereoisomeric nitriles **2a**, **4a**, **6a** and **8a** is tedious and could be accomplished after all by preparative chromatographic separation of a mixture of *cis*/*trans*-diastereomers on silica gel. No synthetic approach to the *cis*-compounds is reported up to now and our efforts to synthesize the pure *cis*-isomers resulted in a 13:1 ratio at best for **2a** (Table 3) to nearly 1:1 for compound **6a** (Scheme 3). The rate difference found in the microbial transformation of *cis*- versus *trans*-isomers is, therefore, for the purpose of a diastereospecific preparation, of great practical use.

This diastereodiscrimination was found to be more distinct in case of the benzoates compared to the tosylates, thus nitriles **2a** and **4a** are not converted at all. Unexpectedly, the conversion rates in general were found to be faster for the tosylated substrates.

To demonstrate the preparative value, larger scale biotransformations were carried out with substrates chosen according to the best screening results in Table 1. The larger scale biotransformations were carried out with the tenfold substrate concentration in contrast to the screening experiments (10 mM versus 1 mM for the screening). In order to provide comparable conversion results, each reaction was

Table 2. Biotransformations of racemic *N*-protected β-amino nitriles by whole cells—isolated yields[a]

Entry	Substrate[b]	*R. equi* A4			*R. erythropolis* NCIMB 11540			*R.* sp. R 312		
		Nitrile % (ee %)[c]	Amide % (ee %)[c]	Acid % (ee %)[c]	Nitrile % (ee %)[c]	Amide % (ee %)[c]	Acid % (ee %)[c]	Nitrile % (ee %)[c]	Amide % (ee %)[c]	Acid % (ee %)[c]
1	**1a**	0	40 (94)	55 (75)	0	30 (>99)	63 (48)	0	7 (>99)	87 (15)
2	**3a**	38 (99)	22 (56)	36 (>95)[d]	59 (44)	16 (67)	15 (>95)[d]	61 (82)	14 (38)	7 (>95)[d]
3	**5a**	40 (47)	14 (>99)	44 (2)	0	13 (>99)	86 (5)	46 (30)	10 (>99)	34 (14)
4	**6a**	71 (5)	14 (51)	0	50 (16)	49 (15)	0	11 (51)	75 (7)	0
5	**7a**	26 (78)	54 (65)	13 (>99)	24 (98)	56 (59)	15 (97)	33 (47)	42 (77)	16 (87)
6	**8a**	47 (8)	48 (6)	0	50 (10)	41 (8)	0	44 (10)	43 (4)	0
7	**10a**	84 (0)	10 (11)	0	91 (1)	2 (32)	0	73 (0)	25 (6)	0

[a] Yields after chromatographic purification.
[b] Substrate amount given in the Section 4.
[c] Columns and chromatographic conditions for chiral separation are given in the Section 4.
[d] Since both enantiomers were not 100% baseline separated, the ee is given as >95%; the second enantiomer could not be actually detected.

stopped after a scheduled time (24 h), deliberately taking into account a mixture of nitrile, amide and acid. The yields of the remaining nitriles, product-amides and acids are given after isolation and chromatographic purification in Table 2.

Transformation of the benzoates **1a** and **3a** resulted, in consistency with the screening results, in a mixture of amide and acid. However, the purification of isolated amide **3b** turned out to be troublesome due to its poor solubility even in MeOH or DMSO. The tosylated nitriles **8a** and **10a** were transformed exclusively to the amides. Nitrile **10a**, prepared by aza-Baylis-Hillman reaction, is a precursor for α-methylene-β-amino acids. The related oxo-analogous Baylis–Hillman carbonitrile was recently reported to give exclusively the amide by incubation with cells of *Rhodococcus* sp. AJ270.[15] These results are in analogy to our aza-compound **10a**.

We have investigated the hydrolysis of *cis*-2-NHTs-cyclopentane nitrile (**6a**) over prolonged reaction time to find out, whether the transformation can be brought to completeness with regard to the acid (**6c**). These experiments were carried out on a 3 mM level in order to obtain sufficient material for the determination of the ee. In Figure 2, the conversion of **6a** using *Rhodococcus equi* A4 is plotted against the reaction time. On a 1 mM level, however, the acid could be detected as the sole product after prolonged reaction time. This is in agreement with results we obtained from experiments, whereby the extend of conversion of **6a** was determined in dependence on its concentration after a constant reaction time (20 h). In this case, the highest conversions were achieved within a concentration range of 0.9–1.5 mM of substrate. Rising the concentration turned out to be accompanied by a significant drop in conversion. As can be seen from Figure 2, 34% acid could be achieved after an incubation time of 206 h (3 mM). The application of extended reaction time to other substrates, for example nitrile **10a** resulted in 53% isolated yield of the respective amide (**10b**) as the only product after 120 h (70% conversion according to HPLC), though no acid was formed after this time.

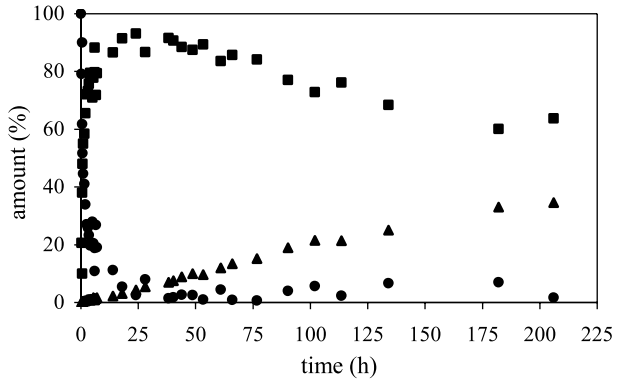


Figure 2. Biotransformation of **6a** by *R. equi* A4 in dependence on reaction time. (●) nitrile; (■) amide; (▲) acid.

Given the rather small structural variation within the *cis*- and *trans*-series of substrates **1**–**8**, the requirement of six different chiral HPLC columns (Chiralcel OD-H, Chiralpak AD-H, Chiralcel OJ, Chiral AGP, Chiral HSA and Chirobiotic R) for the determination of the enantiomeric excess of all products appears rather surprising. In the majority of cases a simultaneous separation of nitrile, amide and/or acid was not feasible. The respective results are included in Table 2. The detailed conditions are given in the Section 4.

Despite this, **3c** could not be resolved on any of the columns mentioned, instead, it was finally resolved by gas chromatographic separation of its methyl ester on Chirasil-Dex CB. Recently the liquid chromatographic separation of unprotected β-amino acids was reported employing a Chirobiotic T column[16] and a chiral crown ether (Crownpak CR(+)).[17] The latter one proved to be more efficient in separating *cis*- and *trans*-amino cyclohexane carboxylic acid, however, the formation of an ammonium ion is a prerequisite for successful separation. No separation of β-amino amides is reported up to now.

The enantioselectivity of the *Rhodococci* towards the *trans*-isomers (**1**, **3**, **5**, **7**) is significantly higher as compared to the *cis*-counterparts (**2**, **4**, **6**, **8**), providing the latter were accepted as substrates at all. Thus, the *trans*-amino cyclohexane carboxylic acids **3c** and **7c** could be prepared by all three microorganisms with very high ee (95–99%), instead, the intermediate amides were formed with moderate ee regardless of their protecting group. Differently, the five-membered *trans*-amides **1b** and **5b** were obtained throughout in very high enantiopurity, but not so their acids. The high enantiomeric purity of the remaining *trans*-nitriles **3a** and **7a** is remarkable, considering the extent of their conversions (38 and 24% resp.). At least for the transformation **3a** to **3b**, this can be attributed to the highly enantioselective nitrile hydratase reported for *Rhodococcus equi* A4.[18]

In Figure 3, the conversion of *cis*-2-NHTs-cyclopentane nitrile (**6a**), amide (**6b**) and acid (**6c**) is plotted versus their enantiomeric excess. Again, the experiments were carried out on a 3 mM level over a reaction time of 206 h. The curve in Figure 3 suggests the enantiopurity-conversion dependence expected from a kinetic resolution. Different from the entries in Table 2, where the acid did not form within the scheduled reaction time of 24 h, 33% acid could be obtained in 34% ee after 206 h. Even at low conversion, the ee of the acid did not exceed 56%. The reasons for that are unknown. One explanation is the presence of an additional amidase acting with opposite enantioselectivity.

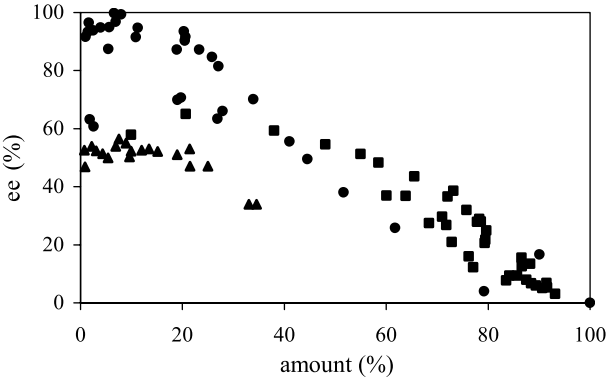
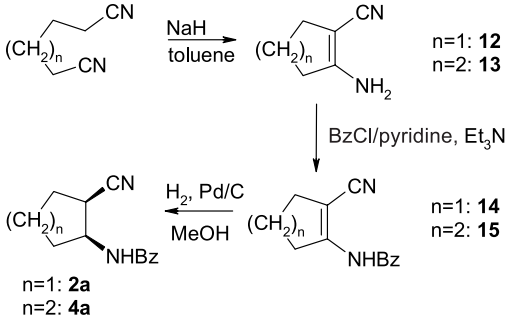


Figure 3. Enantiomeric excess of **6a**–**c** in dependence on conversion by *R. equi* A4. (●) nitrile; (■) amide; (▲) acid.

2.2. Synthesis of substrates

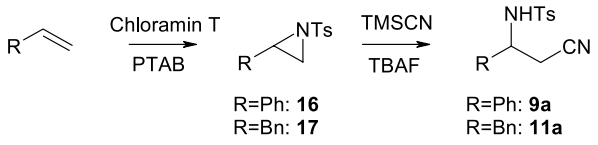
We have made several approaches to prepare **1a**–**4a**, the most preferred one for the *trans*-compounds being via the aziridine ring opening. Generally, the synthetic availability of benzoylated aziridines is limited.[13] However, the benzoylation of the corresponding tosylates with subsequent tosyl-deprotection turned out to be a practicable synthetic protocol for *trans*-compounds **1a** and **3a**, which has already been used in this laboratory for the preparation of Boc-protected amino nitriles.[13] To obtain the *cis*-compounds **2a** and **4a**, we developed a three step synthesis starting from commercially available adiponitrile and heptanedinitrile, respectively. Thorpe–Ziegler cyclization of the latter using NaH yielded unsaturated aminonitriles **12** and **13**.[19]

After benzoylation (BzCl/pyridine) to **14** and **15**, the double bond was catalytically hydrogenated using Pd/C in MeOH at 50 bar and ambient temperature (Scheme 1). The *cis*-selectivity in case of **2a** was 90% after 4 h and 97% conversion and could not be optimized further (Table 3). In the case of the six-membered ring the desired *cis*-compound **4a** could be isolated as a pure diastereoisomer after 3 days under the same conditions at 33% conversion.



Scheme 1.

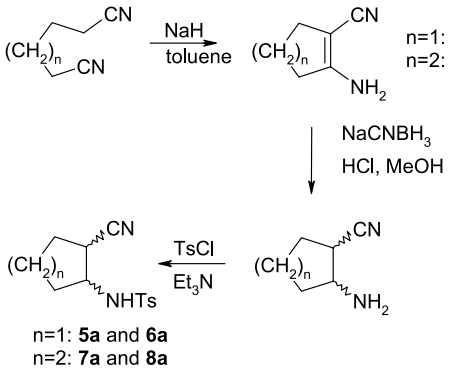
N-Ts-protected compounds **5a** and **7a** were prepared as described in our previous paper.[12] The same methodology was used for **9a** and **11a** via **16** and **17**, respectively,[20] (Scheme 2). The known structure **10a** was prepared by aza-Baylis-Hillman reaction, although the reaction conditions had to be optimized. We applied a number of modifications of the procedure described in the literature,[21] such as variation of the dehydrating agent (molecular sieve 4 Å, PPh_3, DCC, CDI), variation of the base (DABCO, quinuclidine) and the Lewis acid (Ti(i-OPr)$_4$, Sc–, Y–, Yb–, Gd–, La– and In-triflate). GC/MS evaluation revealed



Scheme 2.

that applying other dehydrating agents than molecular sieves partially results in formation of unwanted Baylis–Hillman product, that is the alcohol. Use of quinuclidine resulted in slightly better conversion rates versus DABCO. In-triflate was superior to all the other Lewis acids with respect to conversion and Baylis–Hillman product formation. Summarizing, the price of quinuclidine and In-triflate compared to DABCO and Ti(i-OPr)$_4$ rather suggests an application of the latter reagents.

cis-Tosylates **6a** and **8a** could not be prepared in an analogous way to Scheme 1, since the tosylation of **12** and **13** resulted in complex mixtures and the desired products could only be isolated in yields lower than 5%. Compounds **6a** and **8a** were available through the three step synthesis shown in Scheme 3, followed by silica gel separation of the diastereomers.[22]



Scheme 3.

Reference amides were prepared according to a standard procedure,[23] except **10b**, which was available only through biotransformation.

The chemical hydrolysis to reference acids was attempted by refluxing the corresponding nitriles in NaOH concd. Not surprisingly, the majority of the acids, that is, **1c**–**4c** and **6c**–**8c** could not be prepared by this way. Chemical hydrolysis of **7a** and **8a** resulted in mixtures of nitrile,

Table 3. Optimization of reaction conditions for catalytic hydrogenation of **14**

Entry	Catalyst	Solvent	Pressure (bar)	Time	**14** (%)	**1a** (%)	**2a** (%)
1	Rh/Al_2O_3	MeOH	1	2d	100	0	0
2	10% Pt/C	MeOH	1	2d	100	0	0
3	10% Pd/C	MeOH	1	7d	4	16	80
4	10% Pd/C	Ethyl acetate	1	13d	<1	12	84
5	10% Pd/C	MeOH/H_2O	1	2d	<1	26	74
6	Wilkinson	MeOH	50	4 h	100	0	0
7	5% Pd/C	Ethyl acetate	50	3d	9	17	74
8	5% Pd/C	MeOH	50	20 h	0	21	79
9	5% Pd/C	MeOH	50	4 h	3	7	90

amide and acid, even at reaction times longer than 14 days. *cis*-Nitrile **6a** epimerized under these drastic conditions to the *trans*-acid **5c**.

The benzoylated compounds were deprotected under these conditions. Thus, **2c–4c**, **7c** and **8c** were prepared by protecting the corresponding commercially available carboxylic acids using standard conditions. However, standard tosylation of (±)-cispentacin **18** to (±)-**6c** yielded compound **19**, which was confirmed by NOESY-NMR and single crystal structure (Fig. 4). A proposed mechanism for this reaction path is depicted in Scheme 4, where the amide **19** is generated by aminolysis of the intermediate β-lactam with another molecule of cispentacin **18**. The same side reaction did not occur during the benzoylation of (±)-cispentacin. Thus, the carboxylic acid **6c** was solely available by biotransformation.

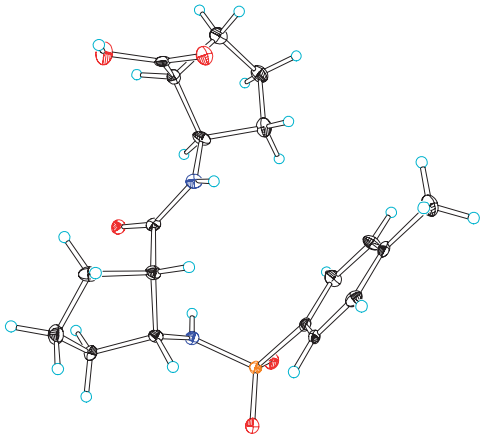


Figure 4. Molecular structure of **19** with thermal ellipsoids at the 30% probability level.

trans-2-Amino cyclopentane carboxylic acid **1c** was prepared by TFA-catalyzed deprotection of (±)-*trans*-2-*tert*-butoxycarbonylamino cyclopentane carboxylic acid[13] and subsequent benzoylation. (±)-2-[Phenyl-(toluene-4-sulfonylamino)-methyl]-acrylic acid **10c** could neither be prepared by chemical nor enzymatic hydrolysis under the above mentioned conditions.

To our knowledge, **1a–c**, **2a–c**, **4a**, **6a–c**, **8a–b**, **10b**, **15** and **19** have not been reported elsewhere up to now. Their spectroscopic data as well as other physical data are given in the Section 4.

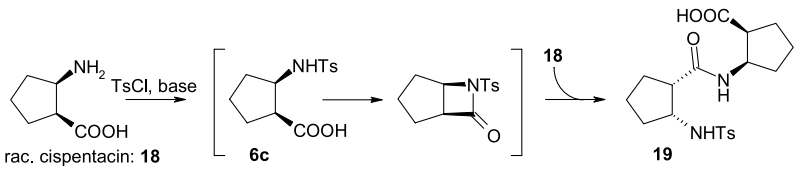
3. Conclusion

The biotransformation of five-membered alicyclic 2-amino nitriles proceeds significantly faster than in case of the six-membered compounds. More specific, the products of the *trans*-2-amino nitriles (amides and acids) are formed considerably faster than the products of the *cis*-counterparts (only amides). With exception of the α-methylene-β-amino carbonitrile structure, which is exclusively transformed to the amide, the other open chain nitriles show no clear trend concerning the formation of a preferred product. These product pattern mentioned in context with the alicyclic substrates (**1–8**) is similar for the three microorganisms investigated. In the same way, the enantioselectivities achieved for the alicyclic compounds are strongly dependent on the structure. Thus, the *trans*-five-membered nitriles give exclusively the amides in excellent enantiopurity (94–99% ee), in contrast, the biotransformation of *trans*-six-membered substrates result in the formation of the acid in excellent enantiopurity (87–99% ee). The ee's of the corresponding *cis*-compounds are throughout lower. The concentration level of the biotransformation reaction was found to exert some influence on the final distribution of the products. As a consequence of the kinetic resolution, improvement of product yield is gained at the expense of the enantiomeric purity.

In summary, the results suggest the application of the investigated *Rhodococci* to the enantioselective hydrolysis of five- and six-membered 2-amino substituted carbocyclic nitriles on a preparative scale.

4. Experimental

Analytical thin layer chromatography was carried out on Merck silica gel 60 F_{254} plates. Flash chromatography was performed on Merck silica gel 60, 230–400 mesh. Analytical HPLC was carried out with a Hewlett Packard Series 1100 HPLC using a G1315A diode array detector or MWD detector. For achiral analysis a LiChrospher 100 RP18e column (5 μm) was used. Chiral analysis was carried out with an Astec Chirobiotic R column, a Chromtech Chiral AGP 100.4 column (5 μm), a Chromtech Chiral HSA 100.4 column (5 μm), a Daicel Chiralpak AD-H (5 μm) and a Chiralcel OD-H column (5 μm). For preparative HPLC a Merck-Hitachi LC-6200 pump and L-4000 UV-detector was used. Separations were performed on a 21.2×250 mm Zorbax SB-C18 preparative HPLC column. CI-mass spectra were recorded with an Agilent 5973N MSD and Agilent 6890 Series II GC. Chiral gas chromatographic analyses were carried out on a Chrompack Chirasil-Dex CB (25 m× 0.32 mm; 0.25 μm film thickness; hydrogen carrier gas). EI-mass spectra were recorded with a Hewlett-Packard 5972 MSD and HP 6890 Series II GC equipped with a HP5 column. ^{1}H NMR (199.98 MHz) and ^{13}C NMR (50.29 MHz) spectra were recorded on a Varian GEMINI-200BB. ^{1}H (499.82 MHz) and ^{13}C NMR (125.69 MHz)



Scheme 4.

spectra were recorded on a Varian INOVA 500. 2D-techniques (HSQC, HMBC) as well as DEPT, NOESY, TOCSY and deuterium exchange were used to assist in structure elucidation. Melting points were determined on a Electrothermal MEL-TEMP apparatus and are uncorrected. The elemental analyses were performed on a Heraeus vario EL. X-ray crystal structures were measured on a Bruker AXS SMART APEX CCD diffractometer.

4.1. Microorganisms and cultivation

4.1.1. Microorganisms. *Rhodococcus equi* A4 was isolated in Prague by the group of V. Křen and L. Martínková and is deposited in the Czech Collection of Microorganisms, Masaryk University, Brno, Czech Republic. *Rhodococcus* sp. R312 is commercially available (CBS 717.73). *Rhodococcus erythropolis* NCIMB 11540 was obtained from DSM Research, The Netherlands. *R. equi* A4 was maintained on MPA agarplates. Merck Standard I nutrient agar medium was used for maintainance of *R*. sp R312 and *R. erythropolis* NCIMB 11540 on agarplates.

4.1.2. Cultivation. All strains were cultivated on BSB medium[24] using acetonitrile as the only source of nitrogen. The microorganisms were cultured at 30 °C and 150 rpm in 250 ml shaking flasks, each containing 100 ml of the above described medium. During the exponential phase of growth, the cells were harvested by centrifugation (5500 rpm, 20 min, 4 °C). The cells were washed with phosphate buffer (4.98 g/l Na_2HPO_4, 2.04 g/l KH_2PO_4, pH 7.5) and again centrifuged.

4.1.3. Screening. For screening experiments, 0.5 ml of cell suspension was put into Eppendorf vessels. The substrates were added as 200 mM solutions in DMSO (2.5 μl) to give a final concentration of 1 mM. The reactions were carried out at 32 °C in an Eppendorf Thermomixer at 850 rpm. After 20 h, 50 μl of HCl (1 N) were added. Unreacted nitriles and products were extracted twice with ethyl acetate. Conversions were determined by RP18 HPLC analysis. In the case of the benzoates **1**–**4** the ethyl acetate was removed and the remaining mixture diluted with methanol.

4.2. General procedure for large scale biotransformation

For preparative biotransformations, the cells were resuspended in the above given buffer, usually about 1 g wet cell weight per 10 ml of buffer. The optical density of the cell suspension was intended to be about 50, but as three different strains were used, the OD-value was not reproducible. The substrates were added as solutions in DMSO to give a final concentration of 10 mM. The DMSO portion was 2.5% (v/v) of the total volume. The reaction was performed in a rotary shaker at 150 rpm and 30 °C for 24 h. The biotransformations were stopped by addition of HCl (2 N). After centrifugation, unreacted nitriles as well as products were extracted from the aqueous phase using ethyl acetate. To prevent from losses of precipitated nitrile, amide and acid, the cells were also resuspended in ethyl acetate and again centrifuged. The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. Unreacted nitrile and products were purified by silica gel chromatography.

4.2.1. (±)-2-[Phenyl-(toluene-4-sulfonylamino)-methyl]-acrylamide (10b). *R. equi* A4 (13.8 g wet cells, 150 ml buffer, $OD_{610}=48$). Yield 79 mg (53%) at 70% conversion after 120 h from 141 mg (±)-**10a** (3 mM); *R. equi* A4 (6.0 g wet cells, 60 ml buffer, $OD_{610}=60$). Yield 20 mg (10%, ee=11%) from 187 mg (±)-**10a** (10 mM); *R. ery.* 11540 (0.8 g wet cells, 10 ml buffer, $OD_{610}=46$). Yield 3 mg (2%, ee=32%) from 125 mg (±)-**10a** (40 mM); *R*. sp R312 (5.0 g wet cells, 40 ml buffer, $OD_{610}=77$). Yield 33 mg (25%, ee=6%) from 124 mg (±)-**10a** (10 mM). White solid, mp 199–200 °C; ^{1}H NMR (DMSO-d_6) δ 2.32 (s, 3H), 5.42 (d, 1H, $J=9.8$ Hz), 5.55 (s, 1H), 5.71 (s, 1H), 6.95 (s, 1H, NH_2), 7.04–7.06 (m, 2H), 7.14–7.19 (3H, m), 7.25 (d, 2H, $J=8.3$ Hz), 7.48 (s, 1H, NH_2), 7.54 (d, 2H, $J=8.3$ Hz), 8.32 (d, 1H, $J=9.8$ Hz, N*H*); ^{13}C NMR (DMSO-d_6) δ 21.63, 57.44, 118.98, 127.12, 127.75, 127.93, 128.71, 129.94, 139.33, 140.59, 142.96, 144.56, 168.84; (CI, methane) *m*/*z* 331 $(M+1)^+$ (3), 313 (42), 260 (6), 172 (91), 160 (100), 155 (24). Anal. Calcd for $C_{17}H_{18}N_2O_3S$: C, 61.80; H, 5.49; N, 8.48. Found: C, 60.62; H, 5.48; N, 8.04. Chiral separation on Chiralcel OD-H, *n*-heptane/*i*-propanol 50:50, 0.38 ml/min, 15 °C.

4.2.2. (±)-*cis*-2-(Toluene-4-sulfonylamino)-cyclopentane carboxylic acid (6c). *R*. sp R312 (27.0 g wet cells, 250 ml buffer, $OD_{610}=61$). Yield 65 mg (92%) at 100% conversion after 76 h from 66 mg (±)-**6a** (1 mM). White solid, mp 139–141 °C; ^{1}H NMR ($CDCl_3$) δ 1.48–1.56 (m, 1H), 1.65–1.82 (m, 3H), 1.88–2.00 (m, 2H), 2.43 (s, 3H), 2.91 (dt, 1H, $J=5.7$, 7.7 Hz, H-1), 3.78 (m, 1H, $J=8.1$ Hz, H-2), 6.16 (d, 1H, $J=9.3$ Hz, N*H*), 7.30 (d, 2H, $J=8.3$ Hz), 7.76 (d, 2H, $J=8.3$ Hz), 5.70 (s, br, 1H, COO*H*); ^{13}C NMR ($CDCl_3$) δ 21.78, 21.95, 28.06, 31.89, 46.55, 56.50, 127.31, 130.01, 137.77, 143.75, 178.46. Anal. Calcd for $C_{13}H_{17}NO_4S$: C, 55.12; H, 6.05; N, 4.94. Found: C, 55.11; H, 5.99; N, 4.97. Chiral separation on Chirobiotic R, polar organic mode (MeOH/Et_3N/AcOH 100:0.4:0.1), 0.80 ml/min, ambient temperature.

4.3. General procedure for benzoylation and detosylation

To a solution of **5a** or **7a** in anhydrous CH_3CN 3.0 equiv of benzoylchloride and DMAP were added. After refluxing for 4 h the solvent was removed under reduced pressure. The remaining oil was diluted with CH_2Cl_2 and washed with saturated NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 three times. The combined organic layers were dried with Na_2SO_4 and concentrated to give a crude oil, which was used for detosylation without further purification. Thus, the oil was dissolved in anhydrous MeOH. After addition of 5.0 equiv of magnesium turnings, the mixture was sonicated for 15 min. The mixture was allowed to react for another 45 min. Then, it was filtered through a plug of celite and washed with MeOH. The solvent was evaporated and the remaining oil diluted with CH_2Cl_2. The organic layer was washed with HCl (2 N), $NaHCO_3$ satd and brine. After drying with Na_2SO_4 and evaporation, the product was purified using silica gel chromatography.

4.3.1. (±)-*trans*-*N*-(2-Cyano-cyclopentyl)-benzamide (1a). White solid, mp 129–130 °C, ^{1}H NMR ($CDCl_3$) δ 1.70–1.78 (m, 1H), 1.83–1.92 (m, 2H), 1.96–2.03 (m, 1H),

2.15–2.21 (m, 1H), 2.22–2.29 (m, 1H), 2.83 (dt, 1H, J=8.3, 7.1 Hz, H-1), 4.54 (m, 1H, J=7.3 Hz, H-2), 6.46 (d, 1H, J=6.3 Hz, N*H*), 7.42 (m, 2H), 7.51 (t, 1H, J=7.3 Hz), 7.75 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 23.20, 29.62, 31.77, 34.95, 56.40, 121.80, 127.23, 128.88, 132.10, 134.05, 167.80; *m/z* (EI) 213 $(M-1)^+$ (8), 161 (4), 105 (100), 77 (35). Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 71.19; H, 6.59; N, 12.43.

4.3.2. (±)-*trans*-*N*-(2-Cyano-cyclohexyl)-benzamide (3a). White solid, mp 167–168 °C; ^{1}H NMR ($CDCl_3$) δ 1.31–1.39 (m, 1H), 1.47–1.55 (m, 2H), 1.72–1.84 (m, 3H), 2.13–2.16 (m, 2H), 2.82 (dt, 1H, J=3.4, 10.0 Hz, H-1), 4.20 (m, 1H, H-2), 6.23 (d, 1H, J=7.8 Hz, N*H*), 7.44 (m, 2H), 7.52 (m, 1H), 7.78 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 24.00, 24.04, 28.85, 31.66, 34.49, 50.27, 120.73, 127.23, 128.90, 132.02, 134.45, 167.47; *m/z* (EI) 228 M^+ (10), 160 (4), 123 (5), 105 (100), 77 (43). Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 74.16; H, 7.27; N, 12.08. Chiral separation on Chiralcel OD-H, *n*-heptane/*i*-propanol 50:50, 0.38 ml/min, 15 °C.

4.4. General procedure for benzoylation

Analogous to Section 4.3 but pyridine was used as the base.

4.4.1. (±)-*trans*-2-Benzoylamino-cyclopentane carboxylic acid (1c). *R. equi* A4 (7.1 g wet cells, 70 ml buffer, OD_{610}=40): Yield 90 mg (55%, ee=75%) from 150 mg (±)-**1a** (10 mM); *R. ery.* 11540 (8.2 g wet cells, 80 ml buffer, OD_{610}=32). Yield 118 mg (63%, ee=48%) from 171 mg (±)-**1a** (10 mM); *R.* sp R312 (7.9 g wet cells, 70 ml buffer, OD_{610}=46). Yield 192 mg (87%, ee=15%) from 150 mg (±)-**1a** (10 mM). White solid, mp 184–186 °C; ^{1}H NMR (DMSO-d_6) δ 1.53–1.65 (m, 2H), 1.67–1.77 (m, 2H), 1.94–2.00 (m, 2H), 2.76 (dt, 1H, J=8.8, 7.3 Hz, H-1), 4.44 (m, 1H, J=7.4 Hz, H-2), 7.44 (m, 2H), 7.50 (m, 1H), 7.81–7.83 (m, 2H), 8.47 (d, 1H, J=7.8 Hz, N*H*), 12.20 (s, br, 1H, COO*H*); ^{13}C NMR (DMSO-d_6) δ 23.93, 29.35, 33.27, 49.98, 54.87, 127.96, 128.88, 131.80, 135.17, 166.63, 176.72. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 65.86; H, 6.40; N, 5.96. Chiral separation on Chirobiotic R, polar organic mode (MeOH/Et_3N/AcOH 100:0.4:0.1), 0.80 ml/min, ambient temperature.

4.4.2. (±)-*cis*-2-Benzoylamino-cyclopentane carboxylic acid (2c). White solid, mp 187–189 °C; ^{1}H NMR (DMSO-d_6) δ 1.47–1.55 (m, 1H), 1.73–1.86 (m, 3H), 1.87–2.00 (m, 2H), 2.93 (dt, 1H, J=7.3, 7.8 Hz, H-1), 4.55 (m, 1H, J=7.5 Hz, H-2), 7.42 (m, 2H), 7.49 (m, 1H), 7.76–7.78 (m, 2H), 8.17 (d, 1H, J=8.3 Hz, N*H*), 11.96 (s, br, 1H, COO*H*); ^{13}C NMR (DMSO-d_6) δ 22.90, 27.81, 31.50, 47.91, 52.98, 128.09, 128.74, 131.65, 135.58, 166.84, 175.30. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.59; H, 6.47; N, 6.42.

4.4.3. (±)-*trans*-2-Benzoylamino-cyclohexane carboxylic acid (3c). *R. equi* A4 (4.1 g wet cells, 40 ml buffer, OD_{610}=40). Yield 36 mg (36%, ee>95%) from 93 mg (±)-**3a** (10 mM); *R. ery.* 11540 (9.0 g wet cells, 90 ml buffer, OD_{610}=38). Yield 33 mg (15%, ee>95%) from 205 mg (±)-**3a** (10 mM); *R.* sp. R312 (7.0 g wet cells, 60 ml buffer, OD_{610}=54). Yield 11 mg (7%, ee>95%) from 137 mg (±)-**3a** (10 mM). White solid, mp 217–219 °C; ^{1}H NMR (DMSO-d_6) δ 1.12–1.22 (m, 1H), 1.24–1.35 (m, 2H), 1.42 (ddd, 1H, J=12.7, 12.7, 3.4 Hz), 1.69 (m, 2H), 1.79–1.82 (m, 1H), 1.90 (m, 1H), 2.43 (dt, 1H, J=3.3, 11.6 Hz, H-1), 3.98 (m, 1H, H-2), 7.42–7.44 (m, 2H), 7.47–7.51 (m, 1H), 7.76–7.78 (m, 2H), 8.29 (d, 1H, J=8.8 Hz, N*H*), 12.01 (s, br, 1H, COO*H*); ^{13}C NMR (DMSO-d_6) δ 25.08, 25.30, 29.55, 32.67, 48.94, 50.21, 127.91, 128.83, 131.68, 135.55, 166.01, 176.08. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 66.78; H, 6.96; N, 5.62. Chirasil-Dex CB after derivatization with (trimethysilyl) diazomethane; 100 °C (2 min), 5°/min 200 °C (H_2, 1 bar).

4.4.4. (±)-*cis*-2-Benzoylamino-cyclohexane carboxylic acid (4c). White solid, mp 175–176 °C; ^{1}H NMR (DMSO-d_6) δ 1.32–1.41 (m, 2H), 1.49–1.65 (m, 4H), 1.77–1.83 (m, 1H), 1.96–2.02 (m, 1H), 2.74 (m, 1H, H-1), 4.30 (m, 1H, H-2), 7.43 (m, 2H), 7.50 (m, 1H), 7.74–7.76 (m, 2H), 8.00 (d, 1H, J=8.3 Hz, N*H*), 12.22 (s, br, 1H, COO*H*); ^{13}C NMR (DMSO-d_6) δ 22.78, 23.55, 25.49, 29.95, 44.41, 48.19, 128.07, 128.83, 131.72, 135.60, 166.71, 175.52. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 66.72; H, 6.86; N, 5.60.

4.4.5. *N*-(2-Cyano-cyclopent-1-enyl)-benzamide (14). White solid; mp 90–92 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.03 (m, 2H), 2.55 (t, 2H, J=6.8 Hz), 3.22 (t, 2H, J=7.7 Hz), 7.42–7.61 (m, 3H), 7.92 (m, 2H), 8.39 (s, 1H, N*H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.44, 30.33, 33.84, 89.90, 116.62, 127.72, 129.16, 133.03, 133.24, 156.67, 164.90; *m/z* (EI) 211 $(M-1)^+$ (31), 105 (100), 77 (50), 51 (11).

4.4.6. *N*-(2-Cyano-cyclohex-1-enyl)-benzamide (15). White solid; mp 102–104 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.71–1.77 (m, 4H), 2.33 (m, 2H), 3.00 (m, 2H), 7.45–7.58 (m, 3H), 7.83 (m, 2H), 8.20 (s, 1H, N*H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.24, 21.72, 25.69, 27.96, 91.38, 118.30, 127.48, 129.23, 132.82, 133.93, 152.30, 165.25; *m/z* (EI) 226 $(M)^+$ (9), 206 (1), 105 (100), 77 (39), 51 (9).

4.5. General procedure for aziridine formation and ring opening

See Ref. 20.

4.5.1. (±)-2-Phenyl-1-(toluene-4-sulfonyl)-aziridine (16). White solid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.39 (d, 1H, J=4.5 Hz), 2.43 (s, 3H), 2.98 (d, 1H, J=7.3 Hz), 3.78 (dd, 1H, J=7.3, 4.5 Hz), 7.20–7.37 (m, 7H), 7.87 (d, 2H, J=7.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.89, 36.18, 41.28, 126.81, 128.19, 128.55, 128.81, 130.14, 135.20, 135.29, 144.92; *m/z* (EI) 155 (1), 118 (32), 91 (100), 77 (5), 65 (44).

4.5.2. (±)-2-Benzyl-1-(toluene-4-sulfonyl)-aziridine (17). White solid; ^{1}H NMR ($CDCl_3$) δ 2.18 (d, 1H, J=4.9 Hz), 2.43 (s, 3H), 2.69 (dd, 1H, J=14.5, 7.1 Hz), 2.72 (d, 1H, J=7.1 Hz), 2.82 (dd, 1H, J=14.5, 4.9 Hz), 2.96 (tt, 1H, J=7.1, 4.9 Hz), 7.03–7.06 (m, 2H), 7.15–7.18 (m, 3H), 7.22 (d, 2H, J=8.6 Hz), 7.69 (d, 2H, J=8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 21.87, 33.07, 37.73, 41.43, 126.74, 128.11, 128.69,

128.96, 129.83, 135.06, 137.25, 144.56; *m/z* (EI) 287 M^+ (5), 172 (4), 155 (6), 132 (100), 105 (57), 91 (64).

4.5.3. (±)-*trans*-*N*-(2-Cyano-cyclopentyl)-4-methyl benzene sulfonamide (5a). White solid, mp 109–110 °C; ^{1}H NMR ($CDCl_3$) δ 1.44–1.51 (m, 1H), 1.65–1.80 (m, 2H), 1.83–1.90 (m, 1H), 1.93–2.00 (m, 1H), 2.06–2.13 (m, 1H), 2.44 (s, 3H), 2.83 (dt, 1H, J=8.6, 6.2 Hz, H-1), 3.73 (m, 1H, J=6.6 Hz, H-2), 5.72 (d, 1H, J=7.2 Hz, N*H*), 7.35 (d, 2H, J=8.3 Hz), 7.81 (2H, d, J=8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 21.84, 22.88, 29.22, 32.85, 35.89, 58.92, 121.41, 127.49, 130.26, 136.76, 144.36; *m/z* (EI) 264 M^+ (10), 210 (27), 155 (38), 109 (26), 91 (100). Anal. Calcd for $C_{13}H_{16}N_2O_2S$: C, 59.07; H, 6.10; N, 10.60. Found: C, 59.63; H, 6.13; N, 10.63. Chiral separation on Chiralcel AD-H, *n*-heptane/*i*-propanol 50:50, 0.50 ml/min, 15 °C.

4.5.4. (±)-*trans*-*N*-(2-Cyano-cyclohexyl)-4-methyl-benzene sulfonamide (7a). White solid, mp 106–108 °C; ^{1}H NMR ($CDCl_3$) δ 1.25–1.39 (m, 3H), 1.58–1.68 (m, 3H), 1.93–1.97 (m, 1H), 2.01–2.06 (m, 1H), 2.44 (s, 3H), 2.62–2.68 (m, 1H, H-1), 3.35–3.41 (ddt, 1H, J=4.1, 8.3, 8.3 Hz, H-2), 5.23 (d, 1H, J=8.3 Hz, N*H*), 7.34 (d, 2H, J=8.5 Hz), 7.82 (d, 2H, J=8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 21.83, 22.78, 23.14, 27.43, 31.66, 34.69, 52.91, 120.46, 127.46, 130.11, 137.31, 144.19; *m/z* (EI) 278 M^+ (4), 210 (33), 155 (32), 123 (16), 91 (100). Anal. Calcd for $C_{14}H_{18}N_2O_2S$: C, 60.41; H, 6.52; N, 10.06. Found: C, 59.72; H, 6.42; N, 9.51. Chiral separation on Chiralcel OD-H, *n*-heptane/*i*-propanol 50:50, 0.38 ml/min, 15 °C.

4.5.5. (±)-*N*-(2-Cyano-1-phenyl-ethyl)-4-methyl-benzene sulfonamide (9a). White solid, mp 141–142 °C; ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 3H), 2.90 (dd, 1H, J=16.5, 7.0 Hz), 2.95 (dd, 1H, J=16.5, 5.5 Hz), 4.57 (dt, 1H, J=5.5, 7.0 Hz), 5.40 (d, 1H, J=7.0 Hz, N*H*), 7.11–7.13 (m, 2H), 7.24 (d, 2H, J=8.6 Hz), 7.27–7.29 (m, 3H), 7.67 (d, 2H, J=8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 21.80, 26.55, 54.38, 116.69, 126.48, 127.38, 129.22, 129.44, 130.05, 136.70, 137.38, 144.29; *m/z* (EI) 260 (60), 155 (52), 145 (5), 91 (100), 77 (20). Anal. Calcd for $C_{16}H_{16}N_2O_2S$: C, 64.98; H, 5.37; N, 9.33. Found: C, 64.19; H, 5.33; N, 9.26.

4.5.6. (±)-*N*-(1-Benzyl-2-cyano-ethyl)-4-methyl-benzene sulfonamide (11a). White solid, mp 106–107 °C; ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H), 2.57 (dd, 1H, J=16.6, 3.9 Hz), 2.66 (dd, 1H, J=16.6, 6.3 Hz), 2.78 (dd, 1H, J=14.0, 7.6 Hz), 2.90 (dd, 1H, J=14.0, 6.8 Hz), 3.64 (m, 1H), 4.79 (d, 1H, J=7.3 Hz, N*H*), 6.98–7.00 (m, 2H), 7.19–7.23 (m, 5H), 7.55 (d, 2H, J=8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 21.81, 24.39, 40.04, 51.49, 116.95, 127.19, 127.67, 129.19, 129.31, 130.11, 135.20, 136.50, 144.11; *m/z* (EI) 223 (57), 155 (100), 91 (100). Anal. Calcd for $C_{17}H_{18}N_2O_2S$: C, 64.94; H, 5.77; N, 8.91. Found: C, 65.33; H, 5.79; N, 8.80.

4.6. General procedure for cyanoborohydride reduction and protection

To a solution of compound **12** or **13** in MeOH bromocresole green was added and the pH of the solution was adjusted with methanolic HCl till the indicator turned to yellow. $NaCNBH_3$ was added in portions while the pH was kept acidic using methanolic HCl. After stirring 30 min at room temperature, the solvent was removed under reduced pressure. The crude residue was diluted with NaOH (1 N). Solid NaCl was added to give a 10% solution. The aqueous phase was extracted with CH_2Cl_2. The product was removed from the organic phase by extraction with HCl (2 N) (CAUTION! Possible formation of HCN). Subsequently, the aqueous phase was made alkaline with NaOH concd and extracted four times with CH_2Cl_2. After drying with Na_2SO_4, the solvent was removed to give a brown oil which was used for standard tosylation of nitriles (see Section 4.7).

4.7. General procedure for tosylation of amino nitriles

The unprotected amino nitriles were suspended in CH_2Cl_2. 1.1 equiv of tosylchloride and 1.5 equiv of Et_3N were added and the mixture was allowed to react at reflux. The reaction was monitored by TLC. After disappearance of starting material, the organic phase was washed with HCl (2 N), $NaHCO_3$ satd and NaCl satd. After drying with Na_2SO_4 the organic solvent was removed and the products were separated by silica gel chromatography.

4.7.1. (±)-*cis*-*N*-(2-Cyano-cyclopentyl)-4-methyl-benzene sulfonamide (6a). White solid, mp 117–119 °C; ^{1}H NMR ($CDCl_3$) δ 1.57–1.65 (m, 2H), 1.82–1.96 (m, 3H), 1.98–2.04 (m, 1H), 2.44 (s, 3H), 2.83 (ddd, 1H, J=7.3, 6.8, 3.4 Hz, H-1), 3.77 (m, 1H, H-2), 5.29 (d, 1H, J=8.8 Hz, N*H*), 7.33 (d, 2H, J=8.3 Hz), 7.81 (d, 2H, J=8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 20.85, 21.82, 28.28, 30.77, 35.23, 56.18, 119.91, 127.41, 130.15, 137.51, 144.15; *m/z* (EI) 264 M^+ (16), 210 (31), 155 (40), 109 (28), 91 (100). Anal. Calcd for $C_{13}H_{16}N_2O_2S$: C, 59.07; H, 6.10; N, 10.60. Found: C, 59.30; H, 5.88; N, 10.75. Chiral separation on Chiralpak AD-H, EtOH, 0.55 ml/min, 40 °C.

4.7.2. (±)-*cis*-*N*-(2-Cyano-cyclohexyl)-4-methyl-benzene sulfonamide (8a). White solid, mp 133–134 °C; ^{1}H NMR ($CDCl_3$) δ 1.12–1.21 (m, 1H), 1.35–1.52 (m, 3H), 1.53–1.61 (m, 2H), 1.68–1.72 (m, 1H), 1.88–1.91 (m, 1H), 2.37 (s, 3H), 3.01 (m, 1H, H-1), 3.24 (m, 1H, J=4.1 Hz, H-2), 4.91 (d, 1H, J=8.3 Hz, N*H*), 7.25 (d, 2H, J=8.3 Hz), 7.71 (d, 2H, J=8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 21.13, 21.82, 24.80, 27.91, 29.89, 35.76, 52.72, 119.52, 127.11, 130.18, 138.10, 144.08; *m/z* (EI) 278 M^+ (0.1), 210 (1), 155 (2), 123 (4), 91 (100). Anal. Calcd for $C_{14}H_{18}N_2O_2S$: C, 60.41; H, 6.52; N, 10.06. Found: C, 60.60; H, 6.63; N, 10.01. Chiral separation on Chiralpak AD-H, *n*-heptane/*i*-propanol 50:50, 0.5 ml/min, 15 °C.

4.8. General procedure for tosylation of amino acids

The unprotected amino acids were suspended in CH_3CN. 1.1 equiv of tosylchloride and 1.5 equiv of Et_3N were added and the mixture was allowed to react at reflux. The reaction was monitored by TLC. After disappearance of starting material, HCl (2 N) was added and the organic solvent was removed. The aqueous phase was extracted three times with CH_2Cl_2. The carboxylic acids were removed from the aqueous phase by extraction with NaOH (2 N) which was subsequently acidified with HCl (2 N). The product was extracted three times with CH_2Cl_2 and three times with ethyl acetate. After drying with Na_2SO_4, the solvent was

removed to give pure white solids (**7c** and **8c**) or a crude product (**19**), which was purified by silica gel chromatography.

4.8.1. (±)-*trans*-2-(Toluene-4-sulfonylamino)-cyclohexane carboxylic acid (7c). *R. equi* A4 (7 g wet cells, 80 ml buffer, $OD_{610}=53$). Yield 31 mg (13%, ee > 99%) from 223 mg (±)-**7a** (10 mM); *R. ery.* 11540 (7.5 g wet cells, 80 ml buffer, $OD_{610}=39$). Yield 35 mg (15%, ee = 97%) from 223 mg (±)-**7a** (10 mM); *R.* sp. R312 (8.1 g wet cells, 80 ml buffer, $OD_{610}=63$). Yield 39 mg (16%, ee = 87%) from 223 mg (±)-**7a** (10 mM). White solid, mp 175–176 °C; ^{1}H NMR ($CDCl_3$) δ 1.16–1.30 (m, 3H), 1.47–1.55 (m, 1H), 1.67 (m, 2H), 1.96–1.99 (m, 2H), 2.32 (dt, 1H, J = 3.6, 10.5 Hz, H-1), 2.42 (s, 3H), 3.36 (ddt, 1H, J = 3.7, 7.6, 10.5 Hz, H-2), 5.31 (d, 1H, J = 7.6 Hz, N*H*), 7.29 (d, 2H, J = 8.3 Hz), 7.76 (d, 2H, J = 8.3 Hz), 8.25 (s, br, 1H, COO*H*); ^{13}C NMR ($CDCl_3$) δ 21.83, 24.29, 24.52, 28.86, 33.38, 49.68, 54.03, 127.41, 129.86, 137.96, 143.63, 178.87. Anal. Calcd for $C_{14}H_{19}NO_4S$: C, 56.55; H, 6.44; N, 4.71. Found: C, 55.98; H, 6.44; N, 4.52. Chiral separation on Chiralpak AD-H *n*-heptane/ethanol 70:30, 0.80 ml/min, 15 °C.

4.8.2. (±)-*cis*-2-(Toluene-4-sulfonylamino)-cyclohexane carboxylic acid (8c). White solid, mp 155 158 °C; ^{1}H NMR ($CDCl_3$) δ 1.25–1.29 (m, 2H), 1.45–1.49 (m, 2H), 1.54–1.60 (m, 1H), 1.66 (m, 1H), 1.76–1.84 (m, 1H), 2.07 (m, 1H), 2.43 (s, 3H), 2.78 (dt, 1H, J = 4.4, 4.6 Hz, H-1), 3.42 (m, 1H, H-2), 6.01 (d, 1H, J = 9.8 Hz, N*H*), 7.30 (d, 2H, J = 8.3 Hz), 7.76 (d, 2H, J = 8.3 Hz), 9.58 (s, br, 1H, COO*H*); ^{13}C NMR ($CDCl_3$) δ 21.80, 22.21, 24.42, 27.74, 29.89, 45.19, 52.68, 127.12, 129.97, 138.53, 143.60, 178.33. Anal. Calcd for $C_{14}H_{19}NO_4S$: C, 56.55; H, 6.44; N, 4.71. Found: C, 57.82; H, 6.99; N, 4.97.

4.8.3. (±)-*cis*-2-{[*cis*-2-(Toluene-4-sulfonylamino) cyclopentanecarbonyl]-amino}-cyclopentane carboxylic acid (19). White solid, mp 176–177 °C; ^{1}H NMR (DMSO-d_6) δ 1.30–1.44 (m, 2H), 1.45–1.56 (m, 3H), 1.57–1.65 (m, 2H), 1.71–1.78 (m, 4H), 1.83–1.90 (m, 1H), 2.36 (s, 3H), 2.59 (q, 1H, J = 7.4 Hz), 2.8 (q, 1H, J = 7.6 Hz), 3.47 (m, 1H,), 4.27 (m, 1H), 7.32 (d, 1H, J = 6.7 Hz, N*H*), 7.35 (d, 2H, J = 8.0 Hz), 7.57 (d, 1H, J = 8.7 Hz, N*H*), 7.64 (d, 2H, J = 8.0 Hz), 11.95 (s, br, 1H, COO*H*); ^{13}C NMR (DMSO-d_6) δ 21.67, 22.11, 22.37, 27.20, 28.04, 31.98, 32.47, 47.22, 47.78, 52.42, 57.07, 127.31, 130.25, 138.68, 143.20, 172.95, 175.01. Crystal data[25] for $C_{19}H_{26}N_2O_5S$: orthorhombic, space group $P2_12_12_1(19)$, a = 6.3805(13) Å, b = 16.940(3) Å, c = 17.430(4) Å, $\alpha=\beta=\gamma=90°$, V = 1883.9(7) Å^3, Z = 4, d_c = 1.391 g cm^{-1}, μ = 0.206 mm^{-1}, (Mo Kα, λ = 0.71073 Å) T = 100 K, the structure was solved by direct methods and refined by full matrix least squares procedures (SHELXL97): R_1 = 0.0691 and 0.0756 (wR_2 = 0.1321 and 0.1345) for 3326 unique measured reflections. Goodness of fit: 1.277.

4.9. General procedure for Thorpe–Ziegler cyclization

1.05 equiv of NaH was stirred in dry toluene and a solution of adipodinitrile or heptanedinitrile in toluene was added dropwise. The mixture was then refluxed for 3 h. EtOH was added in order to destroy excess NaH. Subsequently, water and acetic acid were added slowly. The organic layer was separated and the aqueous phase extracted three times with ethyl acetate. The combined organic layers were dried with Na_2SO_4 and the solvent was evaporated. The product was purified by recrystallization.

4.9.1. 2-Amino-cyclopent-1-ene carbonitrile (12). Pale brown solid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.90 (m, 2H), 2.47 (m, 4H), 4.50 (s, br, 2H, NH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.19, 31.45, 34.48, 74.61, 119.26, 162.65; *m/z* (EI) 107 (M-1)$^+$ (100), 93 (1), 80 (20), 67 (3), 53 (10).

4.9.2. 2-Amino-cyclohex-1-ene carbonitrile (13). Pale brown solid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.65 (m, 4H), 2.12–2.21 (m, 4H), 4.22 (s, br, 2H, NH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.84, 22.21, 24.48, 28.41, 74.33, 121.17, 156.40; *m/z* (EI) 121 (M−1)$^+$ (61), 93 (100), 81 (7), 66 (25).

4.10. General procedure for catalytic hydrogenation

The catalyst (Pd/5% on charcoal) was added to a solution of the olefin **14** or **15** in MeOH. 1 bar (balloon) or 50 bar (autoclave) of hydrogen were applied after evaporating and purging the vessels three times. The reactions were carried out at room temperature and monitored by GC/MS.

4.10.1. (±)-*cis*-*N*-(2-Cyano-cyclopentyl)-benzamide (2a). White solid, mp 107–109 °C, ^{1}H NMR ($CDCl_3$) δ 1.72–1.82 (m, 2H), 1.95–2.04 (m, 1H), 2.06–2.15 (m, 2H), 2.17–2.22 (m, 1H), 3.39 (dt, 1H, J = 3.9, 7.3 Hz, H-1), 4.56–4.63 (m, 1H, H-2), 6.45 (d, 1H, J = 6.5 Hz, N*H*), 7.44 (m, 2H), 7.52 (m, 1H), 7.80 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.85, 29.02, 30.50, 34.72, 52.63, 120.61, 127.30, 128.93, 132.14, 134.07, 168.03; *m/z* (EI) 214 M$^+$ (10), 161 (3), 105 (100), 77 (36). Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.56; H, 6.55; N, 12.75.

4.10.2. (±)-*cis*-*N*-(2-Cyano-cyclohexyl)-benzamide (4a). White solid, mp 177–178 °C; ^{1}H NMR ($CDCl_3$) δ 1.43 (tq, 1H, J = 3.7, 13.2 Hz), 1.53–1.63 (m, 1H), 1.67–1.75 (m, 3H), 1.92 (m, 2H), 2.06 (m, 1H), 3.48 (m, 1H, H-1), 4.14 (m, 1H, J = 4.0 Hz, H-2), 6.38 (d, 1H, J = 6.8 Hz, N*H*), 7.43–7.47 (m, 2H), 7.52 (m, 1H), 7.78 (d, 2H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 21.48, 24.85, 27.68, 28.84, 34.21, 48.99, 120.30, 127.30, 128.91, 132.14, 134.08, 167.44; *m/z* (EI) 228 M$^+$ (16), 160 (7), 123 (6), 105 (100), 77 (38). Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.69; H, 7.13; N, 12.08.

4.11. General procedure for Aza-Baylis-Hillman reaction

Tosylamide was suspended in i-PrOH together with molecular sieve (4 Å) and 0.15 equiv of DABCO. 1.00 equiv of benzaldehyde, 1.10 equiv of acrylonitrile and 0.75 equiv of Ti(i-OPr)$_4$ were added subsequently. The reaction was stirred at room temperature and monitored by TLC. After 36 h, another 0.75 equiv of Ti(i-OPr)$_4$ were added and the reaction was stirred for another 24 h. Subsequently, the mixture was filtered over celite and washed with *i*-PrOH three times. The solvent was removed and the residue was treated with MeOH and H_2SO_4 (2 N) for

90 min. MeOH was removed under reduced pressure and the aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with $NaHCO_3$ satd, water and brine. After drying with Na_2SO_4 the product was purified by silica gel chromatography.

4.11.1. (±)-*N*-(2-Cyano-1-phenyl-2-propenyl)-4-methylbenzenesulfonamide (10a). White solid, mp 126–127 °C; ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H), 5.06 (d, 1H, J=7.3 Hz), 5.23 (d, 1H, J=7.3 Hz, N*H*), 6.00 (d, 1H, J=1.0 Hz), 6.06 (d, 1H, J=1.0 Hz), 7.11–7.13 (m, 2H), 7.28 (d, 2H, J=8.5 Hz), 7.30–7.32 (m, 3H), 7.71 (d, 2H, J=8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 21.82, 60.03, 116.77, 123.60, 127.08, 127.56, 129.35, 129.52, 130.02, 132.09, 136.35, 137.00, 144.33; *m*/*z* (EI) 260 (24), 157 (100), 155 (38), 91 (89), 77 (20). Anal. Calcd for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97. Found: C, 65.57; H, 5.05; N, 8.95. Chiral separation on AGP, 10 mM phosphatebuffer pH 7.02/acetonitrile 85:15, 0.80 ml/min, 15 °C.

4.12. General procedure for amide formation

100 mg of nitrile was dissolved in 5 ml of MeOH. 5.0 equiv of K_2CO_3 and 1 ml of aqueous H_2O_2 (35%) were added. The reaction was stirred at room temperature and monitored by TLC. After completion, the MeOH was removed under reduced pressure, the aqueous phase diluted with water and the product extracted three times with CH_2Cl_2. After drying with Na_2SO_4 and evaporation of the solvent, the product-amides crystallized as pure white substances.

4.12.1. (±)-*trans*-*N*-(2-Carbamoyl-cyclopentyl)-benzamide (1b). *R. equi* A4 (7.1 g wet cells, 70 ml buffer, OD_{610}=40): Yield 66 mg (40%, ee=94%) from 150 mg (±)-**1a** (10 mM); *R. ery.*11540 (8.2 g wet cells, 80 ml buffer, OD_{610}=32). Yield 55 mg (30%, ee > 99%) from 171 mg (±)-**1a** (10 mM); *R.* sp R312 (7.9 g wet cells, 70 ml buffer, OD_{610}=46). Yield 13 mg (7%, ee > 99%) from 150 mg (±)-**1a** (10 mM). White solid, mp 237–239 °C; ^{1}H NMR (DMSO-d_6) δ 1.52–1.65 (m, 2H), 1.67–1.74 (m, 2H), 1.85–1.91 (m, 1H), 1.92–1.98 (m, 1H), 2.65 (dt, 1H, J=8.3, 7.6 Hz, H-1), 4.34 (m, 1H, J=7.3 Hz, H-2), 6.77 (s, br, 1H, NH_2), 7.27 (s, br, 1H, NH_2), 7.44 (m, 2H), 7.51 (m, 1H), 7.82–7.83 (m, 2H), 8.33 (d, 1H, J=7.8 Hz, N*H*); ^{13}C NMR (DMSO-d_6) δ 24.24, 29.53, 33.41, 50.90, 55.08, 128.00, 128.84, 131.75, 135.33, 166.70, 176.41; *m*/*z* (EI) 232 M^+ (0.5), 188 (3), 187 (13), 127 (20), 105 (100), 77 (58). Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 65.83; H, 6.62; N, 11.49. Chiral separation on AGP, 10 mM phosphate buffer pH 7.00 (with 1 mM dimethyloctylamine), 0.90 ml/min, ambient temperature.

4.12.2. (±)-*cis*-*N*-(2-Carbamoyl-cyclopentyl)-benzamide (2b). White solid, mp 198–199 °C; ^{1}H NMR (DMSO-d_6) δ 1.45–1.55 (m, 1H), 1.73–1.86 (m, 1H), 1.88–1.97 (m, 4H), 2.85 (dt, 1H, J=7.3, 8.3 Hz, H-1), 4.43 (m, 1H, J=7.1 Hz, H-2), 6.87 (s, br, 1H, NH_2), 7.33 (s, br, 1H, NH_2), 7.44 (m, 2H), 7.48–7.51 (m, 1H), 7.74–7.76 (m, 2H), 8.12 (d, 1H, J=7.3 Hz, N*H*); ^{13}C NMR (DMSO-d_6) δ 23.25, 28.66, 32.75, 47.24, 53.17, 127.77, 128.93, 131.73, 135.52, 166.47, 175.96; *m*/*z* (EI) 232 M^+ (0.1), 231 (2), 187 (6), 127 (10), 105 (100), 77 (55). Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 66.47; H, 6.75; N, 11.53.

4.12.3. (±)-*trans*-*N*-(2-Carbamoyl-cyclohexyl)-benzamide (3b). *R. equi* A4 (4.1 g wet cells, 40 ml buffer, OD_{610}=40): Yield 22 mg (22%, ee=56%) from 93 mg (±)-**3a** (10 mM); *R. ery.* 11540 (9.0 g wet cells, 90 ml buffer, OD_{610}=38). Yield 35 mg (16%, ee=67%) from 205 mg (±)-**3a** (10 mM); *R.* sp. R312 (7.0 g wet cells, 60 ml buffer, OD_{610}=54). Yield 20 mg (14%, ee=38%) from 137 mg (±)-**3a** (10 mM). White solid, mp 290–291 °C; ^{1}H NMR (DMSO-d_6) δ 0.87–1.12 (m, 3H), 1.24 (ddt, 1H, J=3.4, 12.9, 12.9 Hz), 1.47 (m, 2H), 1.56 (m, 1H), 1.66 (m, 1H), 2.15 (dt, 1H, J=3.4, 11.6 Hz, H-1), 3.69 (m, 1H, H-2), 6.51 (s, br, 1H, NH_2), 6.90 (s, br, 1H, NH_2), 7.20–7.23 (m, 2H), 7.28 (m, 1H), 7.58 (m, 2H), 7.94 (d, 1H, J=8.8 Hz, N*H*); ^{13}C NMR (DMSO-d_6) δ 25.31, 25.41, 29.73, 33.18, 49.40, 50.46, 127.93, 128.82, 131.66, 135.58, 165.97, 176.13; *m*/*z* (EI) 246 M^+ (1), 201 (4), 141 (14), 105 (100), 77 (67). Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 63.97; H, 7.13; N, 9.89. Chiral separation on HSA, 20 mM phosphate buffer (pH 7.00)/2-propanol 97:3, 0.90 ml/min, ambient temperature.

4.12.4. (±)-*cis*-*N*-(2-Carbamoyl-cyclohexyl)-benzamide (4b). White solid, mp 173–174 °C; ^{1}H NMR (DMSO-d_6) δ 1.29–1.38 (m, 2H), 1.44–1.62 (m, 4H), 1.92–1.99 (m, 2H), 2.57–2.60 (m, 1H, H-1), 4.19 (m, 1H, H-2), 6.86 (s, br, 1H, NH_2), 7.35 (s, br, 1H, NH_2), 7.44 (m, 2H), 7.50 (m, 1H), 7.73–7.76 (m, 2H), 7.91 (d, 1H, J=7.3 Hz, N*H*); ^{13}C NMR (DMSO-d_6) δ 22.50, 23.72, 25.88, 30.00, 44.51, 48.74, 127.84, 128.96, 131.78, 135.59, 166.56, 176.41; *m*/*z* (EI) 245 $(M-1)^+$ (7), 201 (11), 141 (28), 105 (100), 77 (52). Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 64.00; H, 7.02; N, 10.28.

4.12.5. (±)-*trans*-2-(Toluene-4-sulfonylamino)-cyclopentane carboxamide (5b). *R. equi* A4 (7 g wet cells, 80 ml buffer, OD_{610}=56). Yield 32 mg (14%, ee > 99%) from 211 mg (±)-**5a** (10 mM); *R. ery.* 11540 (8.0 g wet cells, 80 ml buffer, OD_{610}=32). Yield 30 mg (13%, ee > 99%) from 211 mg (±)-**5a** (10 mM); *R.* sp. R312 (8.0 g wet cells, 80 ml buffer, OD_{610}=62). Yield 23 mg (10%, ee > 99%) from 211 mg (±)-**5a** (10 mM). White solid, mp 180–181 °C; ^{1}H NMR (DMSO-d_6) δ 1.15–1.22 (m, 1H), 1.38–1.53 (m, 4H), 1.78–1.82 (m, 1H), 2.37 (s, 3H), 2.44 (dt, 1H, J=8.8, 6.8 Hz, H-1), 3.66 (m, 1H, J=7.1 Hz, H-2), 6.72 (s, br, 1H, NH_2), 7.14 (s, br, 1H, NH_2), 7.35 (d, 2H, J=8.1 Hz), 7.61 (d, 1H, J=7.8 Hz, N*H*), 7.65 (2H, d, J=8.1 Hz); ^{13}C NMR (DMSO-d_6) δ 21.68, 24.03, 29.97, 33.47, 51.60, 57.58, 127.23, 130.20, 139.36, 143.06, 176.09; *m*/*z* (EI) 281 $(M-1)^+$ (0.02), 238 (0.1), 155 (7), 127 (100), 110 (27), 91 (89). Anal. Calcd for $C_{13}H_{18}N_2O_3S$: C, 55.30; H, 6.43; N, 9.92. Found: C, 55.21; H, 6.12; N, 9.96. Chiral separation on Chiralcel OD-H, *n*-heptane/*i*-propanol 50:50, 0.38 ml/min, 15 °C.

4.12.6. (±)-*cis*-2-(Toluene-4-sulfonylamino)-cyclopentane carboxamide (6b). *R. equi* A4 (2.9 g wet cells, 30 ml buffer, OD_{610}=38). Yield 13 mg (14%, ee=51%) from 88 mg (±)-**6a** (10 mM); *R. ery.* 11540 (7.5 g wet cells, 70 ml buffer, OD_{610}=29). Yield 96 mg (49%, ee=15%) from 185 mg (±)-**6a** (10 mM); *R.* sp. R312 (5.3 g wet cells, 50 ml buffer, OD_{610}=50). Yield 106 mg (75%, ee=7%) from 132 mg (±)-**6a** (10 mM). White solid, mp 167–168 °C; ^{1}H NMR (DMSO-d_6) δ 1.29–1.39 (m, 2H),

1.43–1.51 (m, 1H), 1.57–1.78 (m, 3H), 2.36 (s, 3H), 2.59 (dt, 1H, J=6.8, 8.1 Hz, H-1), 3.53 (m, 1H, J=6.3 Hz, H-2), 6.92 (s, br, 1H, NH_2), 7.26 (s, br, 1H, NH_2), 7.35 (d, 2H, J=8.1 Hz), 7.40 (d, 1H, J=6.8 Hz, NH), 7.67 (2H, d, J=8.1 Hz); ^{13}C NMR (DMSO-d_6) δ 21.66, 22.10, 27.72, 32.20, 47.56, 57.11, 127.33, 130.23, 138.92, 143.18, 175.55; *m/z* (EI) 281 $(M-1)^+$ (1), 238 (1), 155 (16), 127 (51), 110 (20), 91 (100). Anal. Calcd for $C_{13}H_{18}N_2O_3S$: C, 55.30; H, 6.43; N, 9.92. Found: C, 54.76; H, 6.42; N, 9.23. Chiral separation on Chiralpak AD-H, EtOH, 0.55 ml/min, 40 °C.

4.12.7. (±)-*trans*-2-(Toluene-4-sulfonylamino)-cyclohexane carboxamide (7b). *R. equi* A4 (7 g wet cells, 80 ml buffer, OD_{610}=53). Yield 129 mg (54%, ee=65%) from 223 mg (±)-**7a** (10 mM); *R. ery.* 11540 (7.5 g wet cells, 80 ml buffer, OD_{610}=39). Yield 133 mg (56%, ee=59%) from 223 mg (±)-**7a** (10 mM); *R.* sp. R312 (8.1 g wet cells, 80 ml buffer, OD_{610}=62). Yield 100 mg (42%, ee=77%) from 223 mg (±)-**7a** (10 mM). White solid, mp 212–213 °C; ^{1}H NMR (DMSO-d_6) δ 0.93–1.09 (m, 3H), 1.32–1.39 (m, 1H), 1.44–1.51 (m, 3H), 1.69–1.71 (m, 1H), 2.03 (dt, 1H, J=3.9, 10.8 Hz, H-1), 2.35 (s, 3H), 3.26 (ddt, 1H, J=3.7, 9.3, 10.5 Hz, H-2), 6.70 (s, br, 1H, NH_2), 7.01 (s, br, 1H, NH_2), 7.32 (d, 2H, J=8.0 Hz), 7.42 (d, 1H, J=9.3 Hz, NH), 7.65 (d, 2H, J=8.0 Hz); ^{13}C NMR (DMSO-d_6) δ 21.66, 24.81, 24.84, 29.79, 33.12, 50.44, 53.92, 126.96, 130.04, 140.95, 142.69, 175.55; *m/z* (EI) 252 (1), 155 (10), 141 (100), 124 (55), 91 (83). Anal. Calcd for $C_{14}H_{20}N_2O_3S$: C, 56.74; H, 6.80; N, 9.45. Found: C, 56.77; H, 6.60; N, 9.46. Chiral separation on Chiralcel AD-H, *n*-heptane/ethanol 70:30, 0.80 ml/min, 15 °C.

4.12.8. (±)-*cis*-2-(Toluene-4-sulfonylamino)-cyclohexane carboxamide (8b). *R. equi* A4 (6.9 g wet cells, 60 ml buffer, OD_{610}=76): Yield 85 mg (48%, ee=6%) from 167 mg (±)-**8a** (10 mM); *R. ery.* 11540 (8.5 g wet cells, 80 ml buffer, OD_{610}=38). Yield 98 mg (41%, ee=8%) from 223 mg (±)-**8a** (10 mM); *R.* sp. R312 (8.3 g wet cells, 80 ml buffer, OD_{610}=52). Yield 103 mg (43%, ee=4%) from 223 mg (±)-**8a** (10 mM). White solid, mp 161–162 °C; ^{1}H NMR (DMSO-d_6) δ 1.07–1.19 (m, 3H), 1.39–1.48 (m, 3H), 1.66–1.74 (m, 2H), 2.32–2.35 (m, 1H, H-1), 2.36 (s, 3H), 3.33 (m, 1H, H-2), 6.82 (s, br, 1H, NH_2), 7.24 (s, br, 1H, NH_2), 7.34 (m, 3H), 7.81 (d, 2H, J=7.8 Hz); ^{13}C NMR (DMSO-d_6) δ 21.53, 21.66, 23.67, 25.64, 29.65, 45.44, 52.49, 127.22, 130.18, 139.25, 143.11, 176.08; *m/z* (EI) 252 (0.6), 155 (20), 141 (100), 124 (63), 91 (77). Anal. Calcd for $C_{14}H_{20}N_2O_3S$: C, 56.74; H, 6.80; N, 9.45. Found: C, 56.69; H, 6.87; N, 9.23. Chiral separation on Chiralcel OD-H, *n*-heptane/*i*-propanol 50:50, 0.38 ml/min, 15 °C.

4.12.9. (±)-3-Phenyl-3-(toluene-4-sulfonylamino)-propionamide (9b). White solid, mp 213–214 °C; ^{1}H NMR (DMSO-d_6) δ 2.30 (s, 3H), 2.28–2.46 (m, 2H), 4.62 (dt, 1H, J=6.3, 8.8 Hz), 6.72 (s, br, 1H, NH_2), 7.08–7.14 (m, 5H), 7.18 (d, 2H, J=8.1 Hz), 7.23 (s, br, 1H, NH_2), 7.46 (d, 2H, J=8.1 Hz), 8.18 (d, 1H, J=8.8 Hz, NH); ^{13}C NMR (DMSO-d_6) δ 21.60, 43.44, 55.17, 127.04, 127.43, 127.51, 128.56, 129.86, 139.26, 141.80, 142.77, 171.32; *m/z* (CI, methane) 319 $(M+1)^+$ (2), 260 (100), 172 (69), 155 (17), 148 (41). Anal. Calcd for $C_{16}H_{18}N_2O_3S$: C, 60.36; H, 5.70; N, 8.80. Found: C, 57.97; H, 5.48; N, 8.00.

4.12.10. (±)-4-Phenyl-3-(toluene-4-sulfonylamino)-butyramide (11b). White solid, mp 183–184 °C; ^{1}H NMR (DMSO-d_6) δ 2.10 (d, 2H, J=6.8 Hz), 2.33 (s, 3H), 2.48 (dd, 1H, J=13.7, 7.8 Hz), 2.64 (dd, 1H, J=13.7, 5.4 Hz), 3.65 (m, 1H), 6.84 (s, br, 1H, NH_2), 7.02–7.03 (m, 2H), 7.12–7.18 (m, 3H), 7.22 (d, 2H, J=8.1 Hz), 7.30 (s, br, 1H, NH_2), 7.46 (d, 2H, J=8.1 Hz), 7.59 (d, 1H, J=8.3 Hz, NH); ^{13}C NMR (acetone-d_6) δ 20.73, 38.55, 40.81, 53.05, 126.42, 127.06, 128.44, 129.60, 129.66, 138.36, 138.97, 142.89, 172.69. Anal. Calcd for $C_{17}H_{20}N_2O_3S$: C, 61.43; H, 6.06; N, 8.43. Found: C, 60.69; H, 5.94; N, 8.06.

4.13. General procedure for chemical hydratation of nitriles to carboxylic acids

100 mg of nitrile was suspended in 5 ml of NaOH concd and refluxed overnight. Except for the acids **7c** and **8c**, the saponification was complete. The acid was released by addition of HCl and dilution of the aqueous phase with water. Extraction with CH_2Cl_2 or/and ethyl acetate and drying with Na_2SO_4 generally yielded pure crystals. In some cases, the product had to be purified by recrystallization or silica gel chromatography.

4.13.1. (±)-*trans*-2-(Toluene-4-sulfonylamino)-cyclopentane carboxylic acid (5c). *R. equi* A4 (7 g wet cells, 80 ml buffer, OD_{610}=56). Yield 100 mg (44%, ee=2%) from 211 mg (±)-**5a** (10 mM); *R. ery.* 11540 (8.0 g wet cells, 80 ml buffer, OD_{610}=32). Yield 195 mg (86%, ee=5%) from 211 mg (±)-**5a** (10 mM); *R.* sp. R312 (8.0 g wet cells, 80 ml buffer, OD_{610}=62). Yield 76 mg (34%, ee=14%) from 211 mg (±)-**5a** (10 mM). White solid, mp 124–125 °C; ^{1}H NMR ($CDCl_3$) δ 1.44–1.52 (m, 1H), 1.60–1.76 (m, 2H), 1.78–1.85 (m, 1H), 1.95–2.09 (m, 2H), 2.43 (s, 3H), 2.73 (dt, 1H, J=8.8, 7.5 Hz, H-1), 3.80 (m, 1H, J=7.0 Hz, H-2), 5.19 (d, 1H, J=6.4 Hz, NH), 7.30 (d, 2H, J=8.2 Hz), 7.77 (d, 2H, J=8.2 Hz), 9.20 (s, br, 1H, COOH); ^{13}C NMR ($CDCl_3$) δ 21.80, 23.18, 28.47, 33.71, 50.87, 57.73, 127.53, 129.98, 137.13, 143.92, 179.74. Anal. Calcd for $C_{13}H_{17}NO_4S$: C, 55.11; H, 6.05; N, 4.94. Found: C, 55.27; H, 6.05; N, 4.92. Chiral separation on Chirobiotic R, polar organic mode (MeOH/Et_3N/AcOH 100:0.4:0.1), 0.8 ml/min, ambient temperature.

4.13.2. (±)-3-Phenyl-3-(toluene-4-sulfonylamino)-propionic acid (9c). White solid, mp 149–151 °C; ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 2.83 (dd, 1H, J=16.5, 6.3 Hz), 2.93 (dd, 1H, J=16.5, 6.1 Hz), 4.71–4.75 (m, 1H), 5.74 (d, 1H, J=7.8 Hz, NH), 7.10–7.12 (m, 2H), 7.17 (d, 2H, J=8.3 Hz), 7.19–7.21 (m, 3H), 7.60 (d, 2H, J=8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 21.74, 40.89, 54.20, 126.68, 127.35, 128.16, 128.89, 129.75, 137.33, 139.15, 143.68, 174.90. Anal. Calcd for $C_{16}H_{17}NO_4S$: C, 60.17; H, 5.36; N, 4.39. Found: C, 59.72; H, 5.20; N, 4.42.

4.13.3. (±)-4-Phenyl-3-(toluene-4-sulfonylamino)-butyric acid (11c). White solid, mp 101–103 °C; ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 3H), 2.55 (d, 2H, J=4.9 Hz), 2.79 (dd, 1H, J=13.7, 6.9 Hz), 2.86 (dd, 1H, J=13.7, 7.8 Hz), 3.76 (m, 1H), 5.41 (d, 1H, J=8.3 Hz, NH), 7.01–7.03 (m, 2H), 7.20–7.23 (m, 5H), 9.72 (s, br, 1H, COOH), 7.62 (d, 2H, J=8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 21.78, 37.92, 40.75, 51.91, 127.14, 127.22, 128.97, 129.46, 129.94, 136.87, 137.37,

143.69, 176.47. Anal. Calcd for $C_{17}H_{19}NO_4S$: C, 61.24; H, 5.74; N, 4.20. Found: C, 62.47; H, 5.93; N, 4.16.

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25. CCDC 246741 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Dialkylzinc mediated radical additions to chiral *N*-enoyloxazolidinones in the presence of benzaldehyde. Mechanistic investigation, structural characterization of the resulting γ-lactones☆

Samantha Bazin,[a] Laurence Feray,[a] Nicolas Vanthuyne[b] and Michèle P. Bertrand[a,*]

[a]*Laboratoire de Chimie Moléculaire Organique—UMR 6517, Boite 562—Faculté des Sciences St Jérôme, Université d'Aix-Marseille III, Av. Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France*
[b]*Laboratoire de Stéréochimie Dynamique et Chiralité—UMR "Chirotechnologies: Catalyse et Biocatalyse", Faculté des Sciences St Jérôme, Université d'Aix-Marseille III, Av. Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France*

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Abstract—Diethylzinc was used in the presence of oxygen to mediate radical additions to chiral *N*-enoyloxazolidinones derived from fumaric acid. The synthesis of sterically crowded trisubstituted γ-lactones was achieved through a multicomponent reaction involving *t*-butyl iodide and benzaldehyde in addition to the above mentioned reagents. The domino process includes successively: iodine atom transfer, radical addition, homolytic substitution at zinc, aldol condensation, and lactonization. The diastereoselectivity of the reaction and the structural features of the resulting lactones were investigated. A tentative rationalization is discussed. Comparative experiments carried out with diisopropylzinc were performed.

1. Introduction

In 1998, Ryu demonstrated that the reaction of diethylzinc with oxygen could be used to initiate the reduction of alkyl halides by tributyltin hydride.[1] Since then, our group has been investigating the ability of diethylzinc to mediate radical-polar crossover reactions. We first studied the reactivity of glyoxylic imines,[2] and then we extended our investigations to radical additions to enones.[3] In these reactions, the ethyl radical generated through the reaction of diethylzinc with oxygen acts as the chain carrier. More recently, we have shown that, owing to spin delocalization on the oxygen atom in the intermediate radical, conjugate additions to *N*-enoyloxazolidinones proceeded like additions to enones, that is, they were immediately followed by homolytic substitution at zinc, which generated zinc enolates. The latter were trapped with benzaldehyde to give the corresponding aldols.[4,5] Whereas with enones, the addition/homolytic substitution sequence could be carried out indifferently with Et_2Zn or Et_3B,[6] in the case of *N*-enoyloxazolidinones it required exclusively zinc-mediated conditions.[4,7] It seems that in the presence of Et_3B, homolytic substitution at boron did not occurred.

To extend the domino process to the formation of γ-lactones according to the mechanism depicted in Scheme 1,[8] we selected fumaric acid derived chiral oxazolidinones **1** and **2** (Fig. 1) as substrates.

Sibi and co-workers had previously demonstrated that high regio- and stereo-selectivity could be reached when radical additions to substrates of type **2** were carried out in the presence of Lewis acids.[9,10] However, to avoid problems with the regioselectivity, the symmetrical substrate **1**, with a C_2 axis in the conformation shown in Figure 1, was selected first. For the sake of comparison, and to better understand the mechanism, we also investigated the reactivity of compound **2**.

2. Results and discussion

2.1. Diethylzinc mediated addition of *t*-butyl radical

All the reactions were carried out at −10 °C.[11] Two

☆ See Refs. 27 and 28.

Keywords: Diethylzinc; *N*-Enoyloxazolidinones; γ-Lactones; Radical-polar crossover reaction.
* Corresponding author. Tel.: +33 491288597; fax: +33 491670944; e-mail: michele.bertrand@univ.u-3mrs.fr

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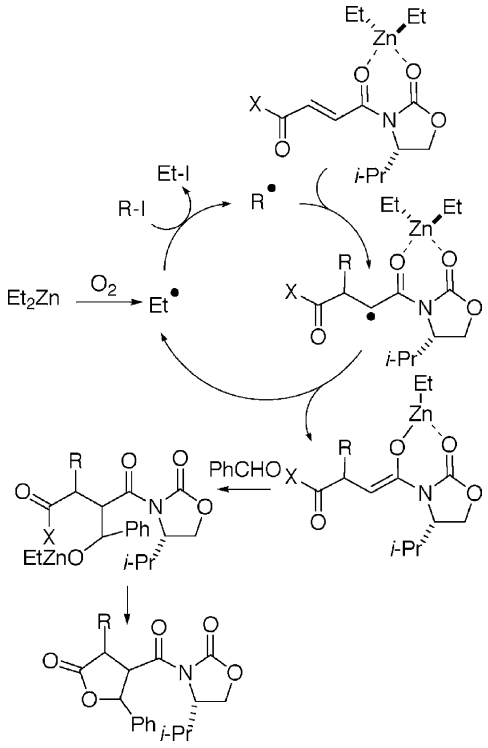


Scheme 1.

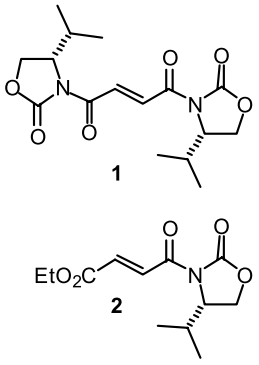
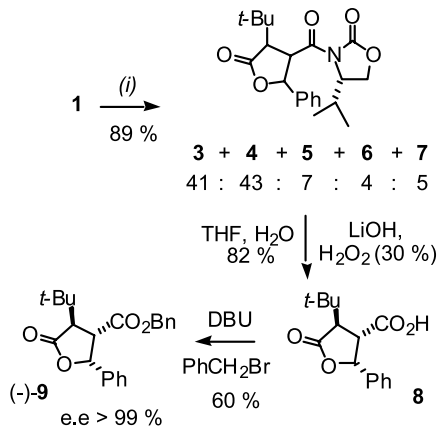


Figure 1.

equivalents of Et_2Zn (1 M solution in hexane) were added to a 0.2 M solution containing either **1** or **2** (1 equiv), benzaldehyde (1.1 equiv) and *t*-BuI (10 or 45 equiv) in dichloromethane. The solution was stirred for 1 h while being injected with 20 mL of air (0.2–0.3 equiv of O_2),[12] and was then allowed to warm up to room temperature before being quenched with aqueous NH_4Cl.

Since a zinc/iodine exchange can be excluded in the case of a tertiary alkyl iodide,[13] *t*-butyl iodide was selected in order to ensure that the process started with a radical pathway. As expected, the use of fumaric derivatives resulted in the stereoselective synthesis of trisubstituted γ-lactones (Scheme 2, Fig. 2 for stereochemical assignments).

It must be noted that when the reaction was carried out with only 10 equiv of *t*-BuI, the lactones resulting from the competitive addition of ethyl radical—7 detectable diastereomers—accounted for approximately 15–18% of the



Scheme 2. (i) $ZnEt_2$ (2 equiv), PhCHO (1.1 equiv), *t*-BuI (45 equiv), CH_2Cl_2, 1 h, air (20 mL), −10 °C.

reaction products. Their total amount was reduced to traces in the presence of a very large excess of the tertiary iodide. The doubly activated double bond was reactive enough with respect to ethyl radical for the radical addition to compete with the fast iodine atom transfer from the tertiary iodide.

Theoretically, eight diastereomers could result from the whole process. Substrate **1** led to a mixture of mainly two diastereomers, **3** and **4**, in nearly equal amounts (Scheme 2, Fig. 2). These two isomers were isolated as pure samples and fully characterized by X-ray spectroscopy.[28] Three minor isomeric lactones (**5**–**7**) were detected from the ^1H NMR spectrum of the mixture. The stereochemistry of **5** was securely determined since it was later isolated as a pure sample when using **2** as starting material (vide infra). The

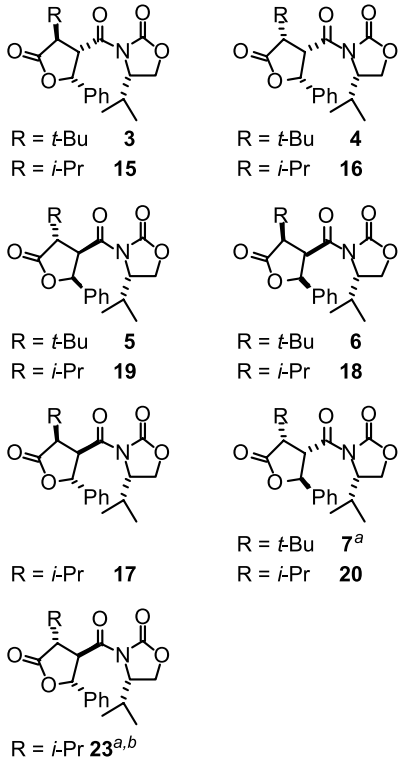
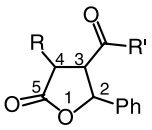


Figure 2. [a]Tentative assignment, based on spectral similarities. [b]The absolute configurations at the lactone ring might be reversed.

stereochemistry of **6** followed from spectral analogies with **4** (characteristic ^{1}H NMR signals were deduced from the analysis of enriched chromatographic fractions). We tentatively assigned the 2,3-*trans*, 3,4-*cis* configuration to **7** (cf. Fig. 2 and Table 1).

Table 1. Chemical shifts and coupling constants of the lactone ring protons in **3**–**11**, **15**–**23**, **25**

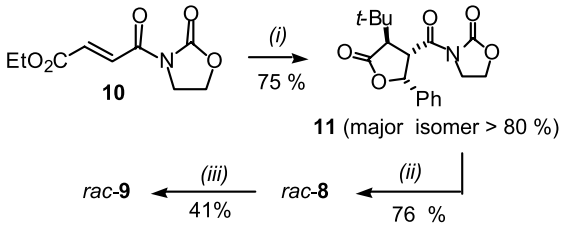


γ-Lactone	δH4 (ppm)	δH3 (ppm)	δH2 (ppm)	J_{34} (Hz)	J_{23} (Hz)
3	3.39	5.07	5.73	6.6	9.4
4	2.89	5.40	5.54	6.4	5.4
5	3.42	4.79	5.89	7.7	9.6
6	2.91	5.45	5.61	6.4	5.2
7	3.19	4.37	5.82	8.5	8.3
8	3.01	3.64	5.65	8.1	9.2
9	3.12	3.70	5.65	7.7	9.2
11[a]	3.36	5.02	5.75	6.4	9.4
15	3.50	4.95	5.78	6.8	9.4
16	2.61	5.36	5.56	6.6	5.7
17	2.97	4.56	5.82	8.7	7
18	2.64	5.39	5.63	6.6	5.6
19	3.56	4.67	5.96	8.3	9.3
20	3.16	4.44	5.84	8.9	7.4
21[a]	3.12	3.61	5.70	8.3	8.9
22	3.23	3.65	5.68	8.1	8.9
23	3.31	5.18	5.29	10.9	9.4
25[a]	3.48	4.88	5.83	6.8	9.2

[a] Major isomer.

The preparative interest of the method was further improved through the cleavage of the remaining auxiliary, carried out on the crude mixture, which, much to our surprise, led to **8** as a single isomer. To determine its optical purity, **8** was transformed via esterification into the corresponding benzylic ester **9** (the yield of the esterification was modest, 41–42% under standard conditions; it reached 60% when using benzylbromide as the solvent, cf. Section 4).

The enantiomeric excess was higher than 99% according to analytic chiral HPLC (Chiralcel OD-H, cf. Supporting Information[27]) by reference to a racemic sample prepared according to Scheme 3.



Scheme 3. (i) $ZnEt_2$ (2 equiv), PhCHO (1.1 equiv), *t*-BuI (45 equiv), CH_2Cl_2, 1 h, air (20 mL), −10 °C; (ii) LiOH, H_2O_2 (30%); (iii) DIC, DMAP, $PhCH_2OH$.

It is worth noting that attempts to assign the stereochemistries of **3**, **4**, **5**, **8** and **9**, based on the vicinal coupling constants analysis referring to literature data, led to erroneous structures. The compounds taken as references were closely related lactones, including natural products such as nephromopsinic, pertusarinic and nephrosteranic acids.[14] It seems that, compared to these natural products, our lactones contain bulkier substituents which induce significant conformational changes in the five-membered ring. The characteristic chemical shifts and coupling constants of the protons in the lactone ring are summarized in Table 1.[15] The absolute configurations of the ring carbons in lactones **3**, **4** and **5** were unambiguously confirmed by X-ray analysis. In the case of lactones **8** and **9**, the 2,3-*cis*, 3,4-*trans* relative configuration was confirmed by NOESY (cf. Supporting Information[27]).

Pure samples of **3** and **4** were isolated and treated separately with $LiOH/H_2O_2$, and both led to the same enantiomer of **8**. This means that epimerization at C4 occurred prior to the cleavage of the auxiliary. Apparently, although there was no control of the facial selectivity during the addition of *t*-butyl radical (55:45), the condensation of both diastereomeric zinc enolates with benzaldehyde resulted in a good level of control of the absolute configuration at both C3 (89:11) and C2 (84:12). Once the configuration at C2 has been controlled, then the configurations at C4 and C3, are determined via the base-catalyzed epimerization that occurs under thermodynamic control during the cleavage step.

A sequence involving ring opening and subsequent ring closure of the resulting carboxylate via Michael addition, that would induce epimerization at C2 before the auxiliary is cleaved, might be considered to explain the high enantioselectivity. We rather believe that, owing to steric hindrance, the reaction of HOO^- with lactones **5**, **6**, and probably **7** (provided the presumed stereochemical assignment is correct) resulted in the cleavage of the oxazolidinone ring.[16]

We were able to isolate from the non-acidic fraction, the presumed amide-alcohol **12a** that could issue from the opening of the oxazolidinone ring of **6**, or **7** (Fig. 3).[17] Unfortunately **12a** could not be quantified nor fully separated from the oxazolidinone auxiliary.

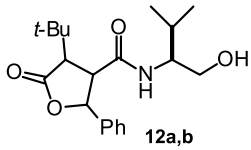


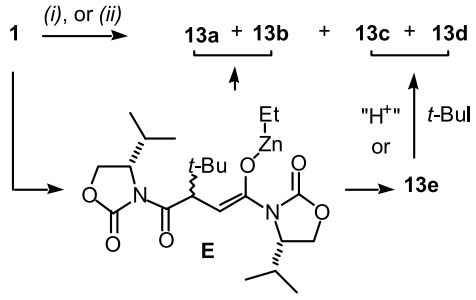
Figure 3.

Additional experiments were conducted on the isolated mixture of lactones resulting from **1** to get evidence of the epimerization process. Treatment with DBU (1 equiv) clearly showed that **4** isomerized into **3**. Because of their low initial amount, we could not ascertain whether lactones **6** or **7** were converted to **5**.

The lack of facial selectivity in the addition of *t*-Bu˙ leads us to recall the results reported by Sibi, who designed a large space demanding substituent on the auxiliary to reach total diastereoselectivity in the radical additions to simple *N*-enoyloxazolidinones carried out in the presence of chelating Lewis acids.[9,10] This lack of selectivity clearly

means that in the presence of diethylzinc the substrates do not keep the conformation shown in Figure 1, which should lead to total control. Thus, in our case, increasing the bulk of the substituent on the auxiliary might be useless.

In order to determine the diastereomeric ratio of the intermediate zinc enolates, «blank» experiments were performed. Compound **1** was allowed to react with diethylzinc and *t*-butyl iodide (45 equiv) in the absence of benzaldehyde.[18] The diastereoselectivity was compared to that observed for the addition of *t*-butyl radical mediated with tributyltin hydride at −10 °C, in the presence of 2 equiv of $ZnCl_2$ (Scheme 4, Fig. 4).[19]



Scheme 4. (i) **13a** (39%)+**13b** (3%)+**13c** (6.5%)+**13d** (24%) (relative ratio=54:5:8:33); (ii) 63% **13a**:**13b**=60:40. (i) $ZnEt_2$ (2 equiv), *t*-BuI (45 equiv), air (20 mL), CH_2Cl_2, 1 h, the yields refer to isolated products; (ii) Bu_3SnH (2 equiv), $ZnCl_2$ (2 equiv), *t*-BuI (5 equiv), BEt_3 (cat), −78 °C.

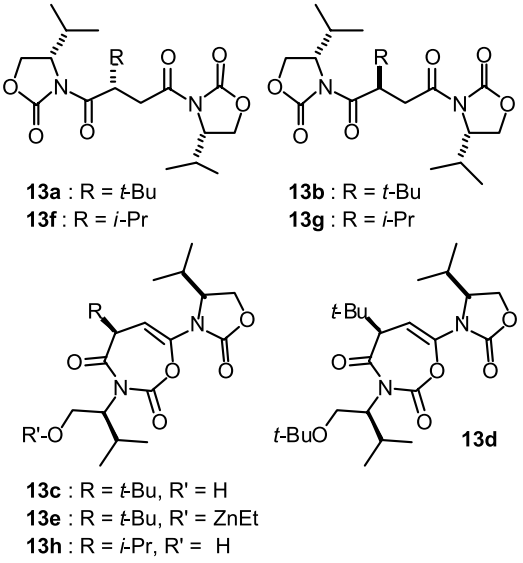
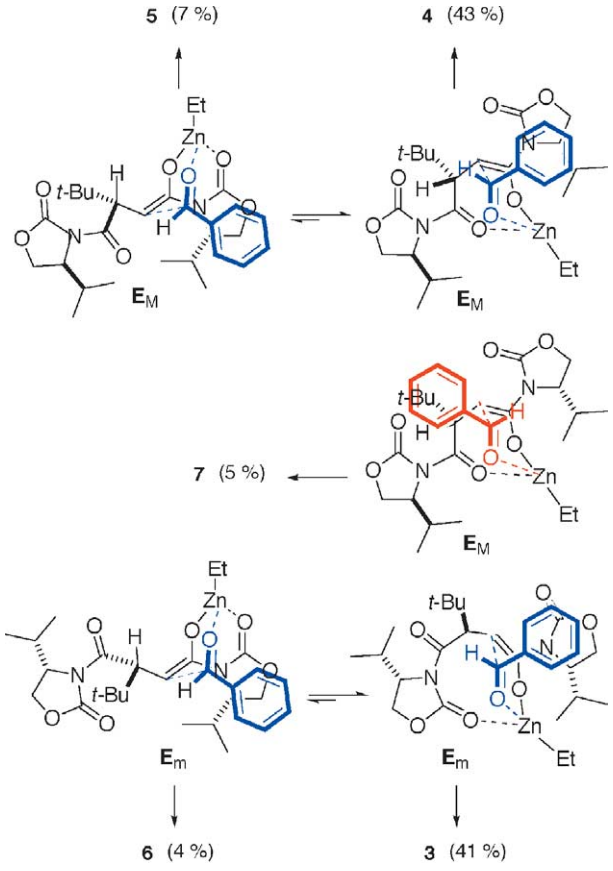


Figure 4.

It was difficult to determine accurately the diastereomeric ratio from the ^1H NMR spectrum of the crude mixture because of overlapping characteristic signals. The ratio was determined after semi-preparative HPLC from the yields in isolated products. Besides one largely predominant diastereomer, which was assigned structure **13a** (**13b** was only detected as trace amount), two unexpected products were formed. Their signals overlapped with the AB part of the ABX pattern characteristic of the methylene α to the carbonyl group in **13a** and **13b** (Scheme 4, Fig. 4). These products, identified as **13c** and **13d** after they were isolated as pure samples, resulted from the same zinc-enolate as **13b** did, via intramolecular nucleophilic displacement. The resulting primary alkoxide **13e** could react slowly with *t*-BuI via either elimination or substitution to give **13c** and **13d**. **13c** also originates from the protonation of **13e** upon treatment with aqueous NH_4Cl. The rearrangement would be prevented in the presence of benzaldehyde, which is more electrophilic than the carbamate.

All these results could be rationalized according to Scheme 5. As shown in Scheme 1, whatever the conformation around the N–C(=O) bond, owing to steric interactions, the preferred conformation around the CH–C(=O) bonds should be *s-cis*, and therefore diastereomeric *Z* enolates should be expected.



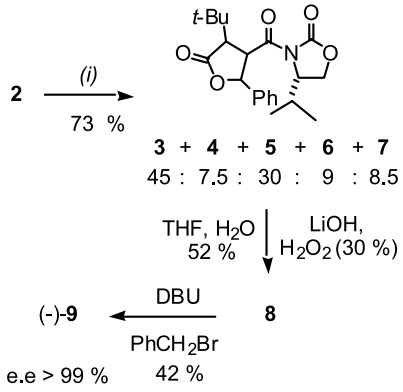
Scheme 5.

The major enolate (E_M) resulting from the attack of *t*-Bu˙ at the *re* face of the double bond would rather adopt a seven-membered chelate structure, than a six-membered chelate one. A similar conformation could not be adopted by the minor enolate (E_m), resulting from the attack of *t*-Bu˙ at the *si* face. The conformational change around the exocyclic N–C(=O) bond would explain why, in the absence of benzaldehyde, this enolate rearranged through nucleophilic displacement at the endocyclic carbonyl group to give **13e** (Fig. 4).

In the presence of benzaldehyde, the preferential approach of the electrophile would be controlled at C3 by the auxiliary attached to the enolate moiety. The control at C2 would be the consequence of the steric bulk and of the

spatial arrangement of the substituents at C4. This arrangement would explain the preference for the Zimmerman–Traxler transition structures shown in Scheme 5, with the phenyl group in a pseudo-axial position rather than for those with the phenyl group in a pseudo-equatorial position. The former structures lead to **3**, **4**, **5** and **6**, while the latter lead to **7**.

As shown in Scheme 6, the comparative reaction conducted on oxazolidinone **2** was less selective, particularly regarding the facial selectivity in the aldol condensation. It led mostly to a mixture of **3** and **5**, and also to minor amounts of the three other diastereomers previously detected when starting from **1**. The exact balance for stereocontrol was 54:46 at C4, 52.5:47.5 at C3, and 61:39 at C2. However, the radical addition was totally regioselective, only the carbon bearing the ethoxycarbonyl group was attacked by *t*-Bu˙.

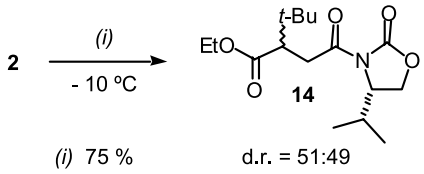


Scheme 6. (i) $ZnEt_2$ (2 equiv), PhCHO (1.1 equiv), *t*-BuI (45 equiv), CH_2Cl_2, 1 h, air (20 mL), −10 °C.

As previously mentioned, the structure of **5** (that could be isolated as a pure sample from this experiment), in which the lactone moiety is the mirror image of the lactone moiety in **3**, could be determined by comparing the chemical shifts and vicinal coupling constants of both lactones, which were quite similar (Table 1). It was unambiguously confirmed by X-ray spectroscopy.[28]

We observed that the cleavage of the remaining auxiliary, followed by the acid-basic extraction performed on the mixture of **3**–**7**, led to **8** (the same enantiomer as that obtained from **1**) but in only 52% yield. As previously, the enantiomeric excess of the corresponding benzylic ester was higher than 99%. Again, owing to epimerization at C4, lactone **4** was converted to **3**. The total amount of **3** and **4** accounted for the lower yield in acid **8**. This indirectly confirmed that the cleavage of lactones **5**, **6** and **7**, that were formed in much larger amounts from **2** than from **1**, led to non-acidic products through the cleavage of the oxazolidinone ring. This is probably due to the sterically hindered exocyclic cleavage, connected to an unfavourable conformation of the auxiliary around the C(O)–N bond.[20] The cleavage of a pure sample of **5** led to a mixture of products: **12b** (Fig. 3), unreacted **5**, and unidentified products.

Again, the selectivity of the reaction is in agreement with the low diastereoselectivity in the addition of *t*-butyl radical (51:49), as witnessed through the experiment described in Scheme 7. It can be noted that the overall diastereomeric ratio in Scheme 6 (**3**+**6**/**4**+**5**+**7**=54:46) supported the configuration assigned to C4 in **7** that would result from the attack of *t*-Bu˙ from the rear.

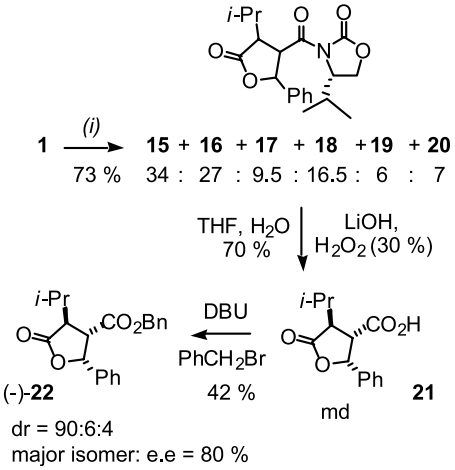


Scheme 7. (i) $ZnEt_2$ (2 equiv), *t*-BuI (45 equiv), air (20 mL), CH_2Cl_2,1 h.

We also investigated the diastereoselectivity of the process when using Et_2Zn alone, in the absence of any alkyl iodide. Due to the presence of oxygen, the radical-polar crossover mechanism is likely, but the contribution of a polar pathway could not be conclusively ruled out. When **1** was used as the substrate, seven lactones resulted from the addition of Et˙.[21] As it was difficult to chromatographically separate pure samples, and as the cleavage of the auxiliary led to a mixture of diastereomeric acids, the investigation of this reaction was not carried further.

2.2. Addition of diisopropylzinc

Attempted addition of *i*-Pr˙ performed by reacting **1** with diethylzinc in the presence of *i*-PrI led to complex mixtures of lactones resulting from both the addition of Et˙ and that of *i*-Pr˙. The diastereoselectivity of the addition of the secondary radical was therefore investigated by reacting **1** and **2** directly with diisopropylzinc and oxygen, in the presence of benzaldehyde. Even though the reaction of dialkylzinc with oxygen is quite fast, the contribution of a polar addition could not be totally ruled out in this case. The results are summarized in Scheme 8.



Scheme 8. (i) Zn(*i*-Pr_2) (2 equiv), PhCHO (1.1 equiv), CH_2Cl_2, 1 h, air (20 mL), −10 °C.

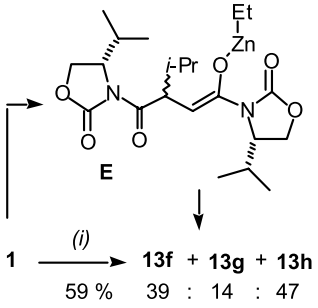
A mixture of six diastereomeric lactones **15**–**20** was isolated (cf. Fig. 2 for stereochemical assignments). Since a complete separation could be achieved in this case through purification by semi-preparative chiral HPLC, yields refer to the isolated products. The two major isomers are likely to have structures similar to those of **3** and **4**. Stereochemical

assignments were made possible by comparing the chemical shifts and coupling constants of H2, H3 and H4 to those of the same protons in **3**–**7** (Table 1). Lactone **19** is likely to have the same structure as **5**. The analysis of the NMR parameters in Table 1 also allowed us to establish structural similitudes between **6** and **18**, and between **7** and **20**. **17** has no structural similitudes with lactones **3**–**7** (the most significant correlations established from the corresponding NOESY spectra are reported in the Supporting Information[27]). The structure of **18** was confirmed by X-ray spectroscopy. The diastereoselectivity reflects an overall 60:40 ratio for *i*-Pr˙ approaching from the front and from the rear, respectively. This ratio is close to that registered for the addition of *t*-Bu˙. However, the secondary radical attacked preferentially the *si* face of the conjugate double bond.

The cleavage of the auxiliary led to **21** (as a mixture of 3 detectable diastereomers). The diastereomeric ratio was confirmed, and the optical purity of the major isomer was determined after esterification. According to ^{1}H NMR, **22** would be a mixture of three diastereomers in a 90:6:4 ratio. The analysis of **22** by chiral HPLC was made by comparing it with a racemic sample prepared from **10** according to a procedure similar to that described for the synthesis of racemic **9**.[22]

We speculate that the lactones bearing an *i*-propyl substituent are less hindered than those bearing a *t*-butyl group, and might well all be cleaved by nucleophilic attack at the exocyclic carbonyl. This would explain why **21** is obtained as a mixture of diastereomers. The epimerization of **16**, and presumably that of **17**, into **15** prior to cleavage would still occur. However, the exocyclic cleavage of **19** would lead to the mirror image of the acid resulting from **15** and this would account for the lower ee (80%) determined after esterification. The exocyclic cleavage of **18** and **20** would contribute to the minor diastereomers of **21**.

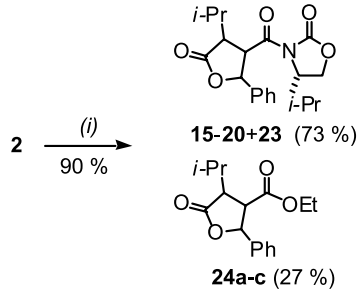
The facial selectivity in the addition of *i*-Pr˙ was confirmed by adding diisopropylzinc alone to **1**. As in the case of the addition of *t*-Bu˙, the zinc enolate precursor of **13g** rearranged via cyclization (Scheme 9) and led to **13h** (Fig. 4) after acid treatment.



Scheme 9. (i) Zn(*i*-Pr$_2$) (2 equiv), air (20 mL), CH_2Cl_2, 2 h, (yields refer to isolated products).

The reaction led to a mixture of diastereomeric adducts, **13g** and **13f**, and to **13h**[23] (Fig. 4) in 59% overall yield. The observed diastereomeric ratio (61:39) corroborated quite well again the 60:40 ratio determined from the mixture of lactones **15**–**20** reported in Scheme 8.

The reaction of **2** with diisopropylzinc led to a complex mixture (Scheme 10). The analysis of the ^{1}H NMR spectrum of the mixture enabled us to identify lactones **15**–**20** and an additional diastereomer **23**.[24] In addition, three regioisomeric lactones **24a**–**c** resulting from the attack of *i*-Pr˙ at the position α to the ethoxycarbonyl group and accounting for approximately 27% of the mixture were also formed.[25]



Scheme 10. Zn(*i*-Pr$_2$) (2 equiv), PhCHO (1.1 equiv), CH_2Cl_2, 1 h, air (20 mL), −10 °C.

The spectral identification is based on the analysis by ^{1}H NMR of enriched fractions of these new products isolated by semi-preparative HPLC. A complete stereochemical assignment could not be achieved for **24a**–**c** which could result from the contribution of a polar mechanism.

3. Conclusion

The dialkylzinc mediated radical additions to fumaric acid derived oxazolidinones carried out in the presence of benzaldehyde led to sterically crowded γ-lactones. The diastereoselectivity is sensitive to the nature of both the substrate and the radical. Regarding asymmetric synthesis, the preparative interest of the method is restricted to the introduction of tertiary alkyl groups. Further investigations of the scope and limitations of the reaction with regard to the nature of the electrophile will be reported in due course.

4. Experimental

4.1. General

NMR, and DEPT spectra were recorded at 300 MHz (^{1}H) and 75 MHz (^{13}C) using $CDCl_3$ as the solvent. The *J* values are given in Hz. Melting point are uncorrected. Column chromatographies were performed on silica gel 60. The solvents for chiral chromatography (*n*-hexane, 2-PrOH, EtOH) are HPLC grade. They were degassed and filtered on Millipore membrane 0.45 μm before use. Cellulose tris(3,5-dimethylphenylcarbamate) chiral stationary phases, CHIRALCEL OD-H (250×4.6 mm) and CHIRALCEL OD (250×10 mm) DAICEL columns are available from Merck-Eurolab. The chiral HPLC analyses were performed on a screening unit composed of Merck D-7000 system manager, Merck-Lachrom L-7100 pump, Merck-Lachrom L-7360 oven, Merck-Lachrom L-7400 UV detector and

on-line chiroptical detectors: Jasco OR-1590 polarimeter or Jasco CD-1595 circular dichroism. The semi-preparative HPLC separations were performed with Merck-Hitachi LiChrograph L-6000 pump, Merck-Hitachi L-4000 UV detector and Merck D-7000 system manager. Detailed chromatographic conditions are reported in the Supporting Information. The optical rotatory powers were measured on a 241 MC Perkin–Elmer polarimeter with a sodium lamp and a double-jacketed cell at 25 °C.

4.1.1. 1,4-Bis-(4(*S*)-*i*-propyl-2-oxo-oxazolidin-3-yl)-but-2-ene-1,4-dione (1). The substrates were prepared according to literature procedures.[26] Methylmagnesium bromide (0.58 mL, 1.7 mmol, 1.1 equiv, 3 M in ether) was added to a solution of 4-isopropyl-oxazolidin-2-one (200 mg, 1.55 mmol) and hydroquinone (2 mg, 0.02 mmol) in 10 mL of anhydrous THF at 0 °C. After stirring for 20 mn at 0 °C, fumaryl chloride (84 μL, 0.78 mmol, 0.5 equiv) was added. The mixture was stirred for 30 mn at room temperature, diluted with 20 mL of ether (peroxide free), and finally washed first with saturated aqueous ammonium chloride, and then with saturated aqueous sodium bicarbonate. The organic layer was dried ($MgSO_4$), and concentrated under reduce pressure. The crude product was purified by FC (10% EtOAc–pentane) leading to **1** as a crystalline solid (382 mg, 1.13 mmol, 73%). Mp 119 °C. ^{1}H NMR (300 MHz): δ 0.83 (d, 6H, J=7.0 Hz), 0.89 (d, 6H, J=7.0 Hz), 2.36 (dsept, 2H, J=4.0, 7.0 Hz), 4.22 (dd, 2H, J=3.2, 9.0 Hz), 4.32 (t, 2H, J=9.0 Hz), 4.47 (m, 2H), 8.12 (s, 2H). ^{13}C NMR (75 MHz): δ 14.6 (CH_3), 17.9 (CH_3), 28.2 (CH), 58.6 (CH), 63.7 (CH_2), 132.9 (CH), 153.7 (C=O), 163.6 (C=O). $[\alpha]_D^{25}=+152$ (c 1.03, $CHCl_3$). Anal. Calcd for $C_{16}H_{22}N_2O_6$: C, 56.80; H, 6.55; N, 8.28. Found: C, 57.00; H, 6.57; N, 8.28.

4.1.2. 4-(4(*S*)-*i*-Propyl-2-oxo-oxazolidin-3-yl)-4-oxo-but-2-enoic acid ethyl ester (2). Methylmagnesium bromide (0.61 mL, 1.7 mmol, 1.1 equiv, 3 M in ether) was added to a solution of 4-isopropyl-oxazolidin-2-one (212 mg, 1.64 mmol) and hydroquinone (2 mg, 0.02 mmol) in 11 mL of anhydrous THF at 0 °C. After stirring for 20 mn at 0 °C, fumaric ethyl ester mono chloride (267 mg, 1.64 mmol, 1 equiv) was added. The mixture was stirred for 30 mn at room temperature, diluted with 21 mL of ether (peroxide free), and finally washed first with saturated aqueous ammmonium chloride, and then with saturated aqueous sodium bicarbonate. The organic layer was dried ($MgSO_4$), and concentrated under reduce pressure. The crude product was purified by FC (10% EtOAc–pentane) to give **2** (217 mg, 0.85 mmol, 52%) as a yellow oil. ^{1}H NMR (300 MHz): δ 0.89 (d, 3H, J=7.0 Hz), 0.94 (d, 3H, J=7.0 Hz), 1.33 (t, 3H, J=7.2 Hz), 2.43 (dsept, 1H, J=3.4, 7.0 Hz), 4.27 (q, 2H, J=7.2 Hz), 4.28 (dd, 1H, J=3.4, 8.3 Hz), 4.36 (t, 1H, J=8.3 Hz), 4.44 (dt, 1H, J=8.3, 3.4 Hz), 6.85 (d, 1H, J=15.5 Hz), 8.09 (d, 1H, J=15.5 Hz). ^{13}C NMR (75 MHz): δ 14.0 (CH_3), 14.5 (CH_3), 17.8 (CH_3), 28.2 (CH), 58.5 (CH), 61.2 (CH_2), 63.6 (CH_2), 132.3 (CH), 134.0 (CH), 153.5 (C=O), 163.6 (C=O), 164.8 (C=O). $[\alpha]_D^{25}=+89$ (c 1.02, $CHCl_3$). Anal. Calcd for $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.39; H, 6.71; N, 5.44.

4.2. General procedure for the synthesis of lactones

Method A. Benzaldehyde (1.1 equiv) and *t*-BuI (none, 10, or 45 equiv) were added under argon at −10 °C, to a 0.2 M solution of substrate, in dichloromethane. Diethylzinc (2 equiv, 1 M solution in hexane) was then introduced and the reaction was stirred at the same temperature while air (20 mL) was injected through a needle into the solution over 1 h. After stirring overnight at room temperature, the reaction was quenched by aqueous NH_4Cl. The reaction mixture was extracted with CH_2Cl_2 (×3). The organic layer was dried, filtered and concentrated. The crude product was purified by FC. All the reactions were repeated several times giving each time similar yields and reproducible diastereomeric ratios.

Method B. Benzaldehyde (1.1 equiv) was added under argon at −10 °C, to a 0.2 M solution of substrate, in dichloromethane. Diisopropylzinc (2 equiv, 1 M solution in hexane) was then introduced and the reaction was stirred at the same temperature while air (20 mL) was injected through a needle into the solution over 1 h. After completion, the reaction was quenched by aqueous NH_4Cl. The reaction mixture was extracted with CH_2Cl_2 (×3). The organic layer was dried, filtered and concentrated. The crude product was purified by FC.

4.2.1. 3-(4-*tert*-Butyl-5-oxo-2-phenyl-tetrahydro-furan-3-carbonyl)-4-*i*-propyl-oxazolidin-2-one (3 and 4). Treating **1** (50 mg, 0.148 mmol) according to method A, in the presence of *t*-butyl iodide (45 equiv, 795 μL), led to **3** and **4** together with small amounts of three other diastereomers (**5**, **6**, **7**) (49 mg, 0.13 mmol, 89%) isolated after purification by FC (5–20%, EtOAc–pentane). The diastereomeric ratio (41:43:7:4:5) was determined from ^{1}H NMR. A second chromatography on silica gel (15–25 μmesh; 2% EtOAc–pentane) allowed the isolation of pure samples of **3** and **4** (order of elution **3**, **4**, **5**, **6**, **7**). Anal. Calcd for $C_{21}H_{27}NO_5$ (mixture of **3**+**4**): C, 67.54; H, 7.29; N, 3.75. Found: C, 67.50; H, 7.54; N, 3.60.

4.2.2. [3*S*-(4*R*-2*R*)-4*S*] (3). Mp 96 °C. ^{1}H NMR (300 MHz): δ 0.74 (d, 3H, J=6.8 Hz), 0.77 (d, 3H, J=6.8 Hz), 1.14 (s, 9H), 2.12 (dsept, 1H, J=4.0, 6.8 Hz), 3.39 (d, 1H, J=6.6 Hz), 3.51 (t, 1H, J=8.3 Hz), 3.58 (ddd, 1H, J=1.7, 4.0, 8.3 Hz), 3.95 (dd, 1H, J=1.7, 8.3 Hz), 5.07 (dd, 1H, J=6.6, 9.4 Hz), 5.73 (d, 1H, J=9.4 Hz), 7.17–7.23 (m, 2H), 7.30–7.37 (m, 3H). ^{13}C NMR (75 MHz): δ 14.7 (CH_3), 17.7 (CH_3), 27.4 (CH_3), 28.6 (CH), 33.4 (C), 47.9 (CH), 51.2 (CH), 58.7 (CH), 63.5 (CH_2), 78.7 (CH), 126.5 (CH), 128.3 (CH), 129.1 (CH), 136.0 (C), 153.8 (C=O), 169.8 (C=O), 176.1 (C=O). $[\alpha]_D^{25}=+15$ (c 1.04, $CHCl_3$).

4.2.3. [3*S*-(4*S*-2*R*)-4*S*] (4). Mp 271–273 °C. ^{1}H NMR (300 MHz): δ 0.76 (d, 3H, J=7.0 Hz), 0.79 (d, 3H, J=7.0 Hz), 1.15 (s, 9H), 2.14 (dsept, 1H, J=4.0, 7.0 Hz), 2.89 (d, 1H, J=6.4 Hz), 3.29 (t, 1H, J=8.5 Hz), 3.60 (ddd, 1H, J=2.1, 4.0, 8.5 Hz), 3.87 (dd, 1H, J=2.1, 8.5 Hz), 5.40 (dd, 1H, J=6.4, 5.4 Hz), 5.54 (d, 1H, J=5.4 Hz), 7.30–7.40 (m, 5H). ^{13}C NMR (75 MHz): δ 14.6 (CH_3), 17.8 (CH_3), 28.7 (CH), 29.3 (CH_3), 31.2 (C), 47.8 (CH), 54.9 (CH), 58.5 (CH), 63.3 (CH_2), 79.2 (CH), 125.5 (CH), 128.2 (CH), 128.4

(CH), 134.8 (C), 153.6 (C=O), 169.1 (C=O), 173.9 (C=O). $[\alpha]_D^{25} = +62$ (*c* 0.59, $CHCl_3$).

4.2.4. (2*R*-3*S*-4*R*) 4-*tert*-Butyl-5-oxo-2-phenyl-tetrahydro-furan-3-carboxylic acid (8). H_2O_2 (30%) (141 μL, 1.4 mmol) and $LiOH.H_2O$ (22 mg, 0.52 mmol) were added at 0 °C to a solution of the isomeric mixture of **3–7** obtained from **1** (129 mg, 0.346 mmol) in THF (2.3 mL) and H_2O (0.6 mL). The mixture was stirred for 1 h at 0 °C. After completion, the excess of H_2O_2 was reduced by addition of an aqueous solution of $Na_2S_2O_3$ (10%). THF was removed under reduce pressure at room temperature. The residual aqueous solution (pH=12) was then extracted with EtOAc (×5). The combined organic phases were dried over $MgSO_4$, concentrated and purified by semi-preparative HPLC. This led to isolate a mixture of **12a** and the auxiliary oxazolidinone. The aqueous phase was then acidified with HCl (10%) up to pH=1 and extracted with EtOAc (×5). The extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduce pressure to give **8** (74 mg, 0.282 mmol, 82%) mp 223 °C. $[\alpha]_D^{25} = -19.6$ (*c* 0.57, $CHCl_3$).^{1}H NMR (300 MHz): δ 1.10 (s, 9H), 3.01 (d, 1H, J=8.0 Hz), 3.64 (dd, 1H, J=8.0, 9.2 Hz), 5.65 (d, 1H, J=9.2 Hz), 7.19–7.27 (m, 5H). ^{13}C NMR (75 MHz): δ 27.4 (CH_3), 33.2 (C), 49.2 (CH), 51.4 (CH), 78.2 (CH), 125.8 (CH), 128.3 (CH), 128.8 (CH), 135.8 (C), 174.0 (C=O), 175.8 (C=O). Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.82; H, 6.79.

4.2.5. 4-*tert*-Butyl-5-oxo-2-phenyl-tetrahydro-furan-3-carboxylic acid ((*S*)-1-hydroxymethyl-2-methyl-propyl-amide (12a). ^{1}H NMR (300 MHz): δ 0.80 (d, 3H, J=6.8 Hz), 0.81 (d, 3H, J=6.6 Hz), 1.15 (s, 9H), 1.69 (m, 1H), 2.86 (m, 1H), 3.20–3.36 (m, 2H), 3.23 (superimposed d, 1H, J=5.5 Hz), 3.43 (dd, 1H, J=8.9, 5.5 Hz), 5.56 (br s, 1H), 5.59 (d, 1H, J=8.9 Hz), 5.71 (br d, 1H, J=8.5 Hz).

^{13}C NMR (75 MHz): δ 17.6 (CH_3), 18.0 (CH_3), 27.6 (3× CH_3), 28.7 (CH), 33.6 (C), 50.4 (CH), 52.7 (CH), 56.6 (CH), 62.4 (CH_2), 79.9 (CH), 126.6 (CH), 128.2 (CH), 128.8 (CH), 136.4 (C), 169.4 (C=O), 176.5 (C=O). HRMS calcd for $C_{20}H_{29}NO_4Na$ [MNa^+]: 370.1994; found: 370.1988.

4.2.6. (2*R*-3*S*-4*R*) 4-*tert*-Butyl-5-oxo-2-phenyl-tetrahydro-furan-3-carboxylic acid benzyl ester (9). A mixture of **8** (53 mg, 0.20 mmol, 1 equiv), benzyl bromide (47 μL, 0.39 mmol, 2 equiv) and DBU (45 μL, 0.30 mmol, 1.5 equiv) in benzene (1 mL) was stirred at 60 °C for 2 h. After cooling to room temperature, insoluble materials were filtered off. The filtrate was concentrated under reduce pressure. The residue was purified on silica gel (10% EtOAc–pentane) to give **9** (30 mg, 42%).

In an alternative procedure, a mixture containing **8** (15 mg, 0.06 mmol, 1 equiv), benzyl bromide (1 mL) and DBU (13 μL, 0.09 mmol, 1.5 equiv) was stirred at room temperature for 7 days. The mixture was directly purified by chromatography on silica gel (100% pentane, then 5% AcOEt–pentane) to give **9** (12 mg, 60%). The enantiomeric excess was determined by chiral HPLC on CHIRALCEL OD-H (250×4.6 mm): hexane–2-PrOH (90:10), 1 mL/min, 25 °C, UV and circular dichroïsm detection at 254 nm, Rt(−)=6.88 min, Rt(+)=7.45 min, $k(-)$=1.28, $k(+)$=1.48, α=1.15 and Rs=1.17.

^{1}H NMR (300 MHz): δ 1.09 (s, 9H), 3.12 (d, 1H, J=7.7 Hz), 3.70 (dd, 1H, J=7.7, 9.2 Hz), 4.62 (AB pattern, 2H, J=12.1 Hz, $\Delta\nu$=61.9), 5.65 (d, 1H, J=9.2 Hz), 7.06–7.36 (m, 10H). ^{13}C NMR (75 MHz): δ 27.4 (CH_3), 33.2 (C), 49.5 (CH), 51.3 (CH), 67.3 (CH_2), 78.5 (CH), 125.8 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 128.8 (CH), 134.6 (C), 136.0 (C), 169.9 (C=O), 175.9 (C=O). $[\alpha]_D^{25} = -20$ (*c* 1.03, $CHCl_3$). HRMS calcd for $C_{22}O_4H_{25}$ [MH^+]: 353.1753; found: 353.1769.

4.2.7. 3-(4-*tert*-Butyl-5-oxo-2-phenyl-tetrahydro-furan-3-carbonyl)-4-*i*-propyl-oxazolidin-2-one (5). Treating **2** (67 mg, 0.26 mmol) according to method A, in the presence of *t*-butyl iodide (45 equiv, 1.4 mL), led to a mixture of **3–7** (76 mg, 0.20 mmol, 73%) isolated after purification by FC (2–10% EtOAc–pentane). The diastereomeric ratio was determined by ^{1}H NMR. A second chromatography allowed the isolation of a pure sample of **5**. Anal. Calcd for $C_{21}H_{27}NO_5$ (mixture): C, 67.53; H, 7.29; N, 3.75. Found: C, 67.41; H, 7.41; N, 3.67.

4.2.8. [3*R*-(4*S*-2*S*)-4*S*] (5). Mp 139–141 °C. ^{1}H NMR (300 MHz): δ 0.24 (d, 3H, J=6.8 Hz), 0.66 (d, 3H, J=6.8 Hz), 1.09 (s, 9H), 1.53 (dsept, 1H, J=2.0, 6.8 Hz), 3.42 (d, 1H, J=7.7 Hz), 4.08–4.23 (m, 3H), 4.79 (dd, 1H, J=7.7, 9.6 Hz), 5.89 (d, 1H, J=9.6 Hz), 7.22–7.35 (m, 5H). ^{13}C NMR (75 MHz): δ 14.3 (CH_3), 18.0 (CH_3), 27.4 (CH_3), 28.3 (CH), 33.4 (C), 47.8 (CH), 51.7 (CH), 59.1 (CH), 63.7 (CH_2), 79.0 (CH), 127.2 (CH), 128.6 (CH), 129.1 (CH), 135.9 (C), 153.8 (C=O), 169.5 (C=O), 175.9 (C=O). $[\alpha]_D^{25} = +85$ (*c* 0.59, $CHCl_3$).

4.2.9. 4-*tert*-Butyl-5-oxo-2-phenyl-tetrahydro-furan-3-carboxylic acid ((*S*)-1-hydroxymethyl-2-methyl-propyl-amide (12b). Treating **5** (16 mg, 0.043 mmol) with LiOH (1.5 equiv, 0.064 mmol, 3 mg) and H_2O_2 (4 equiv, 0.172 mmol, 18 μL) in THF (500 μL) and H_2O_2 (125 μL), led after acid-basic extraction and purification by liquid chromatography on silicagel (95:5 to 60:40, pentane–EtOAc) to 10 mg of a mixture of products containing unreacted starting material, unidentified products, and **12b**. Unfortunately, **12b** could not be fully separated from the other products. The structure was assigned from the ^{1}H NMR of an enriched chromatographic fraction.

^{1}H NMR (300 MHz) characteristic signals of **12b**: δ 0.65 (d, 3H, J=7.0 Hz), 0.70 (d, 3H, J=6.8 Hz), 1.14 (s, 9H), 1.90–2.02 (m, 2H), 3.13 (d, 1H, J=6.4 Hz), 3.20–3.28 (m, 1H), 3.30–3.50 (m, 2H), 3.42 (superimposed dd, 1H, J=6.4, 8.9 Hz), 5.42 (br d, 1H, J=7.7 Hz), 5.60 (d, 1H, J=8.9 Hz), 7.25–7.40 (m, 5H).

4.2.10. 4-(2-Oxo-oxazolidin-3-yl)-4-oxo-but-2-enoic acid ethyl ester (10). Methylmagnesium bromide (4.34 mL, 12.3 mmol, 1.1 equiv, 3 M in ether) was added to a solution of oxazolidin-2-one (1 g, 11.5 mmol) and hydroquinone (15 mg, 0.02 mmol) in 73 mL of anhydrous THF at 0 °C. After stirring for 20 mn at 0 °C, fumaric ethyl ester mono chloride (1.87 g, 11.5 mmol, 1 equiv) was added. The mixture was stirred for 30 mn at room temperature, diluted

with 150 mL of ether (peroxide free), and finally washed first with saturated aqueous ammmonium chloride, and then with saturated aqueous sodium bicarbonate. The organic layer was dried ($MgSO_4$), and concentrated under reduce pressure. The crude product was purified by FC (20% EtOAc–pentane) to give **10** (1.08 g, 5.1 mmol, 45%) as a solid. Mp 62–63 °C. ^{1}H NMR (300 MHz): δ 1.27 (t, 3H, J=7.2 Hz), 4.07 (t, 2H, J=8.1 Hz), 4.20 (q, 2H, J=7.2 Hz), 4.46 (t, 2H, J=8.1 Hz), 6.85 (d, 1H, J=15.7 Hz), 8.05 (d, 1H, J=15.7 Hz). ^{13}C NMR (75 MHz): δ 13.8 (CH_3), 42.3 (CH_2), 61.1 (CH_2), 62.3 (CH_2), 131.7 (CH), 133.6 (CH), 153.0 (C=O), 163.4 (C=O), 164.5 (C=O). Anal. Calcd for $C_9H_{11}NO_5$: C, 50.71; H, 5.20; N, 6.57. Found: C, 50.60; H, 5.23; N, 6.46.

4.2.11. 3-(4-*tert*-Butyl-5-oxo-2-phenyl-tetrahydro-furan-3-carbonyl)-oxazolidin-2-one (11). Treating **10** (43 mg, 0.20 mmol) according to method A, in the presence of *t*-butyl iodide (1.1 mL, 9 mmol), led to **11** (50 mg, 0.15 mmol, 75%) isolated as a mixture of isomers (major isomer >80%) after purification by FC (5–20% EtOAc–pentane). The stereochemistry was assigned according to the analogy of the coupling constants with those observed in **3**. ^{1}H NMR (300 MHz) of major isomer: δ 1.13 (s, 9H), 3.07 (ddd, 1H, J=6.4, 9.3, 10.8 Hz), 3.36 (d, 1H, J=6.4 Hz), 3.72 (ddd, 1H, J=7.0, 9.3, 10.9 Hz), 3.91 (dt, 1H, J=7.0, 9.1 Hz), 4.20 (dt, 1H, J=6.4, 9.1 Hz), 5.02 (dd, 1H, J=6.4, 9.4 Hz), 5.75 (d, 1H, J=9.4 Hz), 7.19–7.23 (m, 2H), 7.30–7.38 (m, 3H). ^{13}C NMR (75 MHz): δ 27.5 (CH_3), 33.4 (C), 42.4 (CH_2), 47.9 (CH), 51.02 (CH) 62.0 (CH_2), 78.8 (CH), 126.3 (CH), 128.4 (CH), 129.0 (CH), 136.0 (C), 153.1 (C=O), 169.9 (C=O), 176.0 (C=O). Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.27; H, 6.45; N, 4.17.

4.2.12. (2*R-3*S**-4*R**) 4-*tert*-Butyl-5-oxo-2-phenyl-tetrahydro-furan-3-carboxylic acid (*rac*-8).** H_2O_2 (30%) (62 μL, 0.60 mmol, 4 equiv) and $LiOH.H_2O$ (9.5 mg, 0.23 mmol, 1.5 equiv) were added at 0 °C to a solution of **11** (50 mg, 0.15 mmol) in THF (2 mL) and H_2O (0.50 mL). The mixture was stirred for 1 h at 0 °C. After completion, the excess of H_2O_2 was reduced by addition of an aqueous solution of $Na_2S_2O_3$ (10%). THF was removed under reduce pressure at room temperature. The residual aqueous solution (pH=12) was then extracted with EtOAc (×5). The aqueous phase was then acidified with HCl (10%) up to pH=1 and extracted with EtOAc (×5). The extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduce pressure to give racemic **8** (30 mg, 0.114 mmol, 76%). The spectrocopic data were identical to those of the optically pure sample previously described.

4.2.13. (2*R-3*S**-4*R**) 4-*tert*-Butyl-5-oxo-2-phenyl-tetrahydro-furan-3-carboxylic acid benzyl ester (*rac*-9).** Diisopropylcarbodiimide (51 μL, 0.33 mmol, 1.64 equiv) was added to a solution of racemic **8** (52 mg, 0.20 mmol, 1 equiv), DMAP (3.77 mg, 0.03 mmol, 0.15 equiv), benzylic alcohol (31 μL, 0.3 mmol, 1.5 equiv) and triethylamine (58 μL, 0.42 mmol, 2.1 equiv) in dichloromethane (760 μL) at 0 °C. The mixture was stirred for 17 h at room temperature. After addition of ethyl acetate to the mixture, the insoluble materials were filtered off through Celite. The filtrate was evaporated to give racemic **9** (23 mg, 0.08 mmol) in 41% yield, as attested by its NMR spectra the crude product was pure enough for analytic purpose. The spectroscopic data were identical to those of the enantiopure sample previously described.

4.2.14. 2-*tert*-Butyl-1,4-bis-((*S*)-4-*i*-propyl-2-oxo-oxazolidin-3-yl)-butane-1,4-dione (13a,b). *t*-BuI (795 μL, 6.67 mmol, 45 equiv) was added under argon at −10 °C, to a 0.2 M solution of substrate **1** (50 mg, 0.15 mmol), in dichloromethane. Diethylzinc (270 μL, 0.27 mmol, 1.8 equiv, 1 M solution in hexane) was then introduced and the reaction was stirred at −10 °C while air (20 mL) was injected through a needle into the solution over 1 h. After completion (1 night), the reaction was quenched by aqueous NH_4Cl. The reaction mixture was extracted with CH_2Cl_2 (×3). The organic layer was dried, filtered and concentrated. The crude product was purified by FC to give a mixture **13a**,**b** and **13d** (together with trace amount of **13c** resulting from the partial protonation of **13e**). Separation by semi-preparative HPLC (CHIRALCEL OD (250×10 mm), hexane–ethanol (90:10), 4.5 mL/min, UV detection at 220 nm) led to the isolation of **13d** (4.12 min, 16 mg), a fraction containing **13b** (5.86 min) and what we assumed to be **13c** (6.90 min) in a 32:68 ratio (5.5 mg), **13a** (8.64 min, 22.9 mg). The yields determined from the above chromatographic separation were: **13a** (39%), **13d** (24%), **13c** (6.5%), **13b** (3%). This would correspond to a 54:46 rear to front selectivity for the addition of *t*-Bu$^{\cdot}$.

Compound **13a**. Mp 219 °C. ^{1}H NMR (300 MHz): δ 0.84 (d, 3H, J=6.8 Hz), 0.86 (d, 3H, J=6.6 Hz), 0.91 (d, 3H, J=7.2 Hz), 0.95 (d, 3H, J=7.0 Hz), 1.01 (s, 9H), 2.22 (septd, 1H, J=6.8, 4.3 Hz), 2.37 (septd, 1H, J=7.0, 3.6 Hz), 3.27 (dd, 1H, J=3.2, 18.3 Hz), 3.45 (dd, 1H, J=11.9, 18.3 Hz), 4.15–4.23 (m, 3H), 4.27 (pseudot, 1H, J=8.9 Hz), 4.35–4.46 (m, 3H). ^{13}C NMR (75 MHz): δ 14.5 (CH_3), 15.1 (CH_3), 17.8 (CH_3), 18.1 (CH_3), 27.5 (CH_3), 28.1 (CH), 28.7 (CH), 33.3 (CH_2), 36.0 (C), 45.4 (CH), 58.4 (CH), 59.2 (CH), 62.7 (CH_2), 63.9 (CH_2), 154.0 (C=O), 154.1 (C=O), 172.3 (C=O), 175.3 (C=O). $[\alpha]_D^{25}=+106.5$ (c 1.01, $CHCl_3$). Anal. Calcd for $C_{20}H_{32}N_2O_6$: C, 60.59; H, 8.14; N, 7.07. Found: C, 60.61; H, 8.16; N, 6.96.

4.2.15. (*R*)-3-((*S*)-1-*tert*-Butoxymethyl-2-methyl-propyl)-5-*tert*-butyl-7-((*S*)-4-*i*-propyl-2-oxo-oxazolidin-3-yl)-5*H*-[1,3]-oxazepine-2,4-dione (13d). ^{1}H NMR (300 MHz): δ 0.79 (d, 3H, J=6.6 Hz), 0.88 (d, 3H, J=7.0 Hz), 0.94 (d, 3H, J=7.0 Hz), 0.96 (d, 3H, J=6.6 Hz), 1.09 (2×s, 18H), 2.18–2.29 (m, 1H), 2.37 (septd, 1H, J=7.0, 4.0 Hz), 3.27 (d, 1H, J=6.4 Hz), 3.52 (dd, 1H, J=8.1, 3.8 Hz), 3.78 (dd, 1H, J=10.5, 8.1 Hz), 3.85 (td, 1H, J=10.5, 4.1 Hz), 4.26 (dd, 1H, J=8.9, 2.3 Hz), 4.37 (dd, 1H, J=8.9, 7.9 Hz), 4.48 (ddd, 1H, J=7.9, 4.0, 2.3 Hz), 5.52 (br d, 1H, J=6.0 Hz). ^{13}C NMR (75 MHz): δ 14.9 (CH_3), 17.9 (CH_3), 19.9 (CH_3), 20.3 (CH_3), 27.1 (CH), 27.3 (CH_3), 27.4 (CH_3), 28.9 (CH), 33.1 (C), 47.1 (=CH), 53.2 (CH), 58.5 (CH_2), 59.4 (2× CH), 63.6 (CH_2), 73.0 (C), 153.9 (C=O), 168.2 (C=), 172.1 (C=O), 177.3 (C=O). Anal. Calcd for $C_{24}H_{40}N_2O_6$: C, 63.69; H, 8.91; N, 6.19. Found: C, 62.92; H, 8.92; N, 5.76. HRMS calcd for $C_{24}H_{40}N_2O_6Na$ [MNa^+]: 475.2784; found: 475.2764.

Characteristic ^{1}H NMR signals of **13c** were deduced from

an enriched chromatographic fraction: δ 1.10 (s, 9H), 2.80 (br s, 1H, OH), 5.6 (br, s, 1H, C═CH).

4.2.16. 2-*tert*-Butyl-1,4-bis-((*S*)-4-*i*-propyl-2-oxo-oxazolidin-3-yl)-butane-1,4-dione (13a,b). To a solution containing **1** (50 mg, 0.148 mmol) and $ZnCl_2$ (40 mg, 0.3 mmol) in a 4:1 mixture of CH_2Cl_2 (3 mL) and THF (740 μL), were added *t*-BuI (0.74 mmol, 89 μL) and Bu_3SnH (0.3 mmol, 80 μL, 2 equiv) at −78 °C. Et_3B (1 M in hexane, 0.3 mmol, 300 μL) was then added via syringe, and then air (7.4 mL) was added with a syringe pump over 15 min. The reaction was stirred for 1 h at −78 °C, then the reaction mixture was diluted with Et_2O (22 mL), washed with 1 M HCl (2× 3 mL) and concentrated. The residue dissolved in CH_2Cl_2 was washed with saturated $Na_2S_2O_3$, the organic phase was dried over $MgSO_4$ and concentrated. After dilution with Et_2O, the solution was stirred with KF (5 equiv) overnight, filtered, concentrated and the residue was purified by flash chromatography (0–50%, EtOAc–pentane) to give **13a** and **13b** in a 60:40 ratio (37 mg, 0.093 mmol, 63%).

4.2.17. 2-[2-((*S*)-4-*i*-Propyl-2-oxo-oxazolidin-3-yl)-2-oxo-ethyl]-3,3-dimethyl-butyric acid ethyl ester (14). Treating **2** (50 mg, 0.196 mmol) with Et_2Zn (0.35 mmol, 353 μL) and *t*-BuI (8.82 mmol, 1.1 mL) according to the procedure already described for the preparation of **13**, led after purification by FC (5–30%, EtOAc–pentane) to **14** (46 mg, 0.147 mmol, 75%) as a nearly 1:1 mixture of diastereomers.

^{1}H NMR (300 MHz): δ 0.87 (d, 6H, J=6.8 Hz), 0.88 (d, 3H, J=6.8 Hz), 0.90 (d, 3H, J=6.8 Hz), 1.00 (s, 9H), 1.01 (s, 9H), 1.26 (t, 3H, J=7.0 Hz), 1.28 (t, 3H, J=7.2 Hz), 2.22–2.42 (m, 2H), 2.65 (dd, 1H, J=12.1, 2.9 Hz), 2.68 (dd, 1H, J=12.1, 2.9 Hz), 3.10 (dd, 1H, J=18.5, 2.9 Hz), 3.14 (dd, 1H, J=18.3, 2.9 Hz), 3.35 (dd, 1H, J=18.9, 12.1 Hz), 3.42 (dd, 1H, J=18.5, 12.1 Hz), 4.04–4.30 (m, 8H), 4.35–4.45 (m, 2H). ^{13}C NMR (75 MHz): δ 14.2 (CH_3), 14.3 (CH_3), 14.6 (CH_3), 14.7 (CH_3), 17.8 (CH_3), 17.9 (CH_3), 28.0 (2× CH_3), 28.3 (CH), 28.4 (CH), 32.5 (C), 32.6 (C), 34.7 (2× CH_2), 50.6 (CH), 50.8 (CH), 58.3 (CH), 58.4 (CH), 60.1 (CH_2), 60.2 (CH_2), 63.4 (CH_2), 63.5 (CH_2), 154.1 (2× C═O), 172.3 (C═O), 172.5 (C═O), 174 (C═O), 174.4 (C═O). HRMS calcd for $C_{16}H_{28}NO_5$ [MH^+]: 314.1967; found: 314.1968.

4.2.18. 3-(4-*i*-Propyl-5-oxo-2-phenyl-tetrahydro-furan-3-carbonyl)-4-*i*-propyl-oxazolidin-2-one (15–20). Treating **1** (100 mg, 0.29 mmol) according to method B led to a mixture of isomeric lactones **15**–**20** (76 mg, 0.215 mmol, 73%) isolated after purification by FC (5–20%, EtOAc–pentane). The diastereomeric ratio (34:9.5:27:16.5:6:7), given by order of elution, was determined on the isolated products after having achieved a complete separation of the mixture by chiral HPLC (CHIRALCEL OD (250×10 mm), hexane–ethanol (80:20), 4.5 mL/min, UV detection at 220 nm). This led by order of elution to **15** (4.90 min, 26.2 mg, 34%), **17** (5.90 min, 7.3 mg, 9.5%), **16** (6.79 min, 20.6 mg, 27%), **18** (9.06 min, 12.7 mg, 16.5%), **19** (10.10 min, 4.6 mg, 6%), **20** (11.45 min, 5.1 mg, 7%). Anal. Calcd for $C_{20}H_{25}NO_5$ (mixture of isomers): C, 66.84; H, 7.01; N, 3.90. Found: C, 66.90; H, 6.95; N, 3.81.

Compound **15**. Mp 125–126 °C. ^{1}H NMR (300 MHz): δ 0.76 (d, 3H, J=6.8 Hz), 0.78 (d, 3H, J=6.8 Hz), 1.04 (d, 3H, J=7.0 Hz), 1.07 (d, 3H, J=7.0 Hz), 2.14 (dsept, 1H, J=4.2, 7.0 Hz), 2.33 (oct, 1H, J=6.8 Hz), 3.47–3.56 (m, 2H), 3.57–3.63 (m, 1H), 3.96 (dd, 1H, J=1.7, 8.5 Hz), 4.95 (dd, 1H, J=6.8, 9.4 Hz), 5.78 (d, 1H, J=9.4 Hz), 7.17–7.25 (m, 2H), 7.31–7.38 (m, 3H). ^{13}C NMR (75 MHz): δ 14.7 (CH_3), 17.7 (CH_3), 18.9 (CH_3), 20.2 (CH_3), 28.5 (CH), 28.8 (CH), 47.3 (CH), 47.5 (CH), 58.8 (CH), 63.5 (CH_2), 79.3 (CH), 127.4 (CH), 128.4 (CH), 129.1 (CH), 135.9 (C), 153.8 (C), 169.5 (C), 177.1 (C). $[\alpha]_D^{25}$ = +4 (*c* 1.02, $CHCl_3$).

Compound **17**. ^{1}H NMR (300 MHz): δ 0.74 (d, 3H, J=6.8 Hz), 0.88 (d, 3H, J=6.8 Hz), 1.04 (d, 3H, J=6.8 Hz), 1.14 (d, 3H, J=6.8 Hz), 2.02 (oct, 1H, J=6.8 Hz), 2.38 (dsept, 1H, J=4.1, 6.9 Hz), 2.97 (dd, 1H, J=5.9, 8.7 Hz), 4.24 (dd, 1H, J=9.3, 3.4 Hz), 4.34 (dd, 1H, J=9.3, 8.3 Hz), 4.35–4.40 (superimposed m, 1H), 4.56 (dd, 1H, J=8.5, 7.0 Hz), 5.82 (d, 1H, J=7.0 Hz), 7.29–7.46 (m, 5H). ^{13}C NMR (75 MHz): δ 14.4 (CH_3), 17.8 (CH_3), 19.7 (CH_3), 21.9 (CH_3), 27.7 (CH), 28.0 (CH), 48.2 (CH), 52.7 (CH), 58.6 (CH), 63.6 (CH_2), 80.1 (CH), 125.4 (CH), 128.8 (CH), 128.6 (CH), 138.0 (C), 153.5 (C═O), 169.5 (C═O), 175.4 (C═O). $[\alpha]_D^{25}$ = −16 (*c* 1.04, $CHCl_3$).

Compound **16**. ^{1}H NMR (300 MHz): δ 0.74 (d, 3H, J=6.8 Hz), 0.78 (d, 3H, J=6.8 Hz), 0.89 (d, 3H, J=6.8 Hz), 1.31 (d, 3H, J=6.8 Hz), 2.11 (dsept, 1H, J=4.3, 6.8 Hz), 2.24 (dsept, 1H, J=10.2, 6.8 Hz), 2.61 (dd, 1H, J=6.6, 10.2 Hz), 3.20 (dd, 1H, J=8.1, 8.9 Hz), 3.64 (ddd, 1H, J=2.1, 4.3, 8.1 Hz), 3.84 (dd, 1H, J=2.1, 8.9 Hz), 5.36 (dd, 1H, J=5.7, 6.6 Hz), 5.56 (d, 1H, J=5.7 Hz), 7.31–7.40 (m, 5H). ^{13}C NMR (75 MHz): δ 15.0 (CH_3), 17.7 (CH_3), 21.3 (CH_3), 21.7 (CH_3), 25.4 (CH), 29.0 (CH), 48.2 (CH), 51.4 (CH), 58.6 (CH), 63.6 (CH_2), 79.0 (CH), 125.6 (CH), 128.3 (CH), 128.4 (CH), 134.9 (C), 153.4 (C═O), 169.0 (C═O), 175.7 (C═O). $[\alpha]_D^{25}$ = +109.4 (*c* 1.02, $CHCl_3$).

Compound **18**. Mp 181 °C. ^{1}H NMR (300 MHz): δ −0.01 (d, 3H, J=7.0 Hz) (the shielding indicates that the protons are held above the aromatic ring as confirmed by X-ray spectroscopy[28]), 0.67 (d, 3H, J=7.0 Hz), 0.84 (d, 3H, J=6.6 Hz), 1.30 (d, 3H, J=6.6 Hz), 1.64 (dsept, 1H, J=2.7, 7.0 Hz), 2.06 (dsept, 1H, J=10.6, 6.6 Hz), 2.64 (dd, 1H, J=6.6, 10.6 Hz), 4.03 (dd, 1H, J=2.7, 9.3 Hz), 4.10 (t, 1H, J=9.3 Hz), 4.25 (dt, 1H, J=9.3, 2.7 Hz), 5.39 (dd, 1H, J=5.6, 6.6 Hz), 5.63 (d, 1H, J=5.6 Hz), 7.24–7.37 (m, 3H), 7.38–7.45 (m, 2H). ^{13}C NMR (75 MHz): δ 13.6 (CH_3), 18.0 (CH_3), 21.2 (CH_3), 21.9 (CH_3), 25.8 (CH), 28.3 (CH), 47.3 (CH), 52.4 (CH), 58.5 (CH), 63.0 (CH_2), 79.3 (CH), 126.0 (CH), 128.4 (CH), 128.5 (CH), 134.4 (C), 153.5 (C═O), 169.1 (C═O), 175.4 (C═O). $[\alpha]_D^{25}$ = +54 (*c* 1.01, $CHCl_3$).

Compound **19**. ^{1}H NMR (300 MHz): δ 0.25 (d, 3H, J=7.0 Hz), 0.66 (d, 3H, J=7.0 Hz), 1.01 (d, 3H, J=7.0 Hz), 1.05 (d, 3H, J=7.0 Hz), 1.51–1.62 (m, 1H), 2.28 (dsept, 1H, J=5.1, 7.0 Hz), 3.56 (dd, 1H, J=5.1, 8.3 Hz), 4.08–4.25 (m, 3H), 4.67 (dd, 1H, J=8.3, 9.3 Hz), 5.96 (d, 1H, J=9.3 Hz), 7.23–7.34 (m, 5H). ^{13}C NMR (75 MHz): δ 14.3 (CH_3), 18.1 (CH_3), 19.0 (CH_3), 20.0 (CH_3), 28.3 (CH), 28.7 (CH), 47.3 (CH), 47.9 (CH), 59.0 (CH), 63.7 (CH_2), 79.6 (CH), 127.2 (CH), 128.6 (CH), 129.2 (CH), 135.8 (C), 153.8 (C═O), 169.0 (C═O), 176.8 (C═O). $[\alpha]_D^{25}$ = +156 (*c* 0.98, $CHCl_3$).

Compound **20**. ^{1}H NMR (300 MHz): δ 0.92 (d, 3H, J= 6.8 Hz), 0.96 (d, 3H, J=6.8 Hz), 1.11 (d, 3H, J=6.8 Hz), 1.15 (d, 3H, J=6.8 Hz), 2.00 (oct, 1H, J=6.8 Hz), 2.39 (dsept, 1H, J=3.6, 6.8 Hz), 3.16 (dd, 1H, J=5.1, 8.9 Hz), 4.22–4.34 (m, 2H), 4.44 (dd, 1H, J=8.9, 7.4 Hz), 4.44 (superimposed pseudo t, 1H, J=8.9 Hz), 5.84 (d, H, J= 7.4 Hz), 7.31–7.45 (m, 5H). ^{13}C NMR (75 MHz): δ 14.6 (CH_3), 18.1 (CH_3), 19.2 (CH_3), 22.2 (CH_3), 28.0 (CH), 29.7 (CH), 48.6 (CH), 53.0 (CH), 58.7 (CH), 63.6 (CH_2), 80.0 (CH), 125.9 (CH), 128.7 (CH), 128.8 (CH), 138.1 (C), 153.5 (C=O), 168.9 (C=O), 175.2 (C=O).

4.2.19. 3-(4-*i*-Propyl-5-oxo-2-phenyl-tetrahydro-furan-3-carbonyl)-4-*i*-propyl-oxazolidin-2-one (15–20+23+ 24a–c). Treating **2** (97 mg, 0.38 mmol) according to method B led to a mixture of lactones that was separated by semi-preparative HPLC (CHIRALCEL OD (250×10 mm), hexane–ethanol (80:20), 4.5 mL/min, UV detection at 220 nm). The separation led, by order of elution to: a first fraction containing **15** and **24a–c** in a 21:79 ratio (27.6 mg); **17** (27 mg); **16** and **23** in a 52:48 ratio (11.7 mg); **18** and **19** in a 90:10 ratio (8 mg); **18** and **19** in a 25:75 ratio (6.1 mg); **19** (23.3 mg), **20** (4.7 mg). The intermediate chromatographic fractions (6.3 mg) remixed together contained **24a–c** (65%), **18** (9%), **19** (16%), **20** (10%). A second separation of the very first fraction allowed to analyze the NMR spectra of **24a–c** (CHIRALCEL OD (250×10 mm), hexane–ethanol (95:5), 4.5 mL/min, UV detection at 220 nm, **24a** (5.79 min), **24b** (6.83 min), **24c** (10.48 min)).

Compound **23**. ^{1}H NMR (300 MHz): δ 0.55 (d, 3H, J= 7.0 Hz), 0.87 (d, 3H, J=7.0 Hz), 0.98 (d, 3H, J=7.0 Hz), 1.06 (d, 3H, J=7.0 Hz), 2.20–2.40 (m, 2H), 3.31 (dd, 1H, J=10.9, 4.2 Hz), 4.12 (dd, 1H, J=9.3, 2.9 Hz), 4.21 (pseudot, 1H, J=9.1 Hz), 4.48 (pseudo dt, 1H, J=8.3, 3.2 Hz), 5.18 (dd, 1H J=10.9, 9.4 Hz), 5.29 (d, 1H, J= 9.4 Hz), 7.32–7.40 (m, 5H). ^{13}C NMR (75 MHz): δ 14.0 (CH_3), 17.9 (CH_3), 18.3 (CH_3), 20.2 (CH_3), 27.6 (CH), 28.3 (CH), 30.9 (CH), 47.8 (CH), 53.0 (CH), 62.9 (CH_2), 83.0 (CH), 126.6 (CH), 128.8 (CH), 129.5 (CH), 135.9 (C), 152.9 (C=O), 171.8 (C=O), 175.2 (C=O).

4.2.20. Ethyl 4-*i*-propyl-5-oxo-2-phenyl-tetrahydro-furan-3-carboxylate (24a–c). *Compound* **24a**. ^{1}H NMR (300 MHz): δ 1.00 (d, 3H, J=6.8 Hz), 1.02 (d, 3H, J= 7.2 Hz), 1.25 (t, 3H, J=7.2 Hz), 2.34 (m, 1H), 3.10 (dd, 1H, J=10.8, 8.3 Hz), 3.17 (dd, 1H, J=10.8, 4.2 Hz), 4.22 (m, 2H), 5.43 (d, 1H, J=8.3 Hz), 7.28–7.40 (m, 5H). ^{13}C NMR (75 MHz): δ 14.9 (CH_3), 19.1 (CH_3), 20.6 (CH_3), 28.6 (CH), 52.0 (CH), 52.3 (CH), 62.5 (CH_2), 81.3 (CH), 126.3 (CH), 129.6 (CH), 129.7 (CH), 138.8 (C), 172.3 (C=O), 176.1 (C=O).

Compound **24b**. ^{1}H NMR (300 MHz): δ 0.91 (t, 3H, J= 7.2 Hz), 1.04 (d, 6H, J=7.0 Hz), 2.30 (m, 1H), 3.21 (dd, 1H, J=7.8, 5.1 Hz), 3.59 (pseudot, 1H, J=8.7 Hz), 3.71 (ABX_3 pattern, 2H), 5.68 (d, 1H, J=9.1 Hz), 7.19–7.42 (m, 5H). ^{13}C NMR (75 MHz): δ 13.6 (CH_3), 18.9 (CH_3), 20.0 (CH_3), 28.4 (CH), 47.5 (CH), 48.7 (CH), 61.2 (CH_2), 79.2 (CH), 125.9 (CH), 128.4 (CH), 128.8 (CH), 135.9 (C), 169.6 (C=O), 176.9 (C=O).

Compound **24c**. ^{1}H NMR (300 MHz): δ 0.85 (t, 3H, J= 7.2 Hz), 0.93 (d, 3H, J=6.8 Hz), 1.31 (d, 3H, J=6.6 Hz), 2.15 (m, 1H), 2.58 (dd, 1H, J=10.2, 6.8 Hz), 3.61 (dd, 1H, J=6.8, 5.7 Hz), 3.75 (ABX_3 pattern, 2H), 5.53 (d, 1H, J= 5.7 Hz), 7.29–7.37 (m, 5H). ^{13}C NMR (75 MHz): δ 13.6 (CH_3), 21.3 (CH_3), 21.7 (CH_3), 26.2 (CH), 51.6 (CH), 52.0 (CH), 60.8 (CH_2), 78.7 (CH), 125.4 (CH), 128.3 (CH), 128.4 (CH), 135.0 (C), carbonyl quaternary carbons were not detected under the registration conditions. HRMS calcd for $C_{16}H_{21}O_4$ [MH^+]: 277.1440; found: 277.1436.

4.2.21. (2*R*-3*S*-4*S*) 4-*i*-Propyl-5-oxo-2-phenyl-tetrahydro-furan-3-carboxylic acid (21). H_2O_2 (30%) (117 μL, 1.14 mmol) and $LiOH.H_2O$ (18 mg, 0.43 mmol) were added at 0 °C to a solution of **15–20** obtained from **1** (86 mg, 0.24 mmol) in THF (2 mL) and H_2O (0.5 mL). The mixture was stirred for 1 h at 0 °C. After completion, the excess of H_2O_2 was reduced by addition of an aqueous solution of $Na_2S_2O_3$ (10%). THF was removed under reduce pressure at room temperature. The residual aqueous solution (pH=12) was then extracted with EtOAc (×3). The aqueous phase was then acidified with HCl (10%) up to pH=1 and extracted with EtOAc (×5). The extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduce pressure to give **21** as a white solid (42 mg, 0.169 mmol, 70%).

^{1}H NMR (300 MHz), major isomer: δ 1.03 (d, 3H, J= 6.8 Hz), 2.26 (dsept, 1H, J=5.3, 6.8 Hz), 3.12 (dd, 1H, J=5.3, 8.3 Hz), 3.61 (dd, 1H, J=8.3, 8.9 Hz), 5.70 (d, 1H, J=8.9 Hz), 7.19–7.40 (m, 5H), 8.24 (br s, 1H). ^{13}C NMR (75 MHz): δ 19.4 (CH_3), 20.4 (CH_3), 28.8 (CH), 48.2 (CH), 49.1 (CH), 79.5 (CH), 126.3 (CH), 128.8 (CH), 128.9 (CH), 136.1 (C), 173.7 (C=O), 177.5 (C=O). HRMS calcd for $C_{14}H_{15}O_4$ [$(M-H)^-$]: 247.0970; found: 247.0977.

4.2.22. (2*R*-3*S*-4*S*) 4-*i*-Propyl-5-oxo-2-phenyl-tetrahydro-furan-3-carboxylic acid benzyl ester (22). A mixture of **21** (42 mg, 0.17 mmol, 1 equiv), benzyl bromide (39 μL, 0.33 mmol, 2 equiv) and DBU (38 μL, 0.25 mmol, 1.5 equiv) in benzene (1 mL) was stirred at 60 °C for 2 h. After cooling to room temperature, insoluble materials were filtered off. The filtrate was concentrated under reduce pressure. The residue was purified on silica gel (10% EtOAc–pentane) to give 24 mg (42%) of ester **22** as a 90:6:4 ratio of diastereomers. The enantiomeric excess of the major isomer (80%) was determined from chiral HPLC (CHIRALCEL OD-H (250×4.6 mm), hexane–2-PrOH (90:10), 1 mL/min, 25 °C, UV and circular dichroïsm detection at 254 nm, Rt(−)=8.16 min, Rt(+)=9.76, k(−)=1.64, k(+)=2.16, α=1.32 and Rs=2.49).

^{1}H NMR (300 MHz): δ 1.02 (d, 3H, J=7.0 Hz), 1.03 (d, 3H, J=7.0 Hz), 2.29 (dsept, 1H, J=5.1, 7.0 Hz), 3.23 (dd, 1H, J=5.1, 8.1 Hz), 3.65 (dd, 1H, J=8.1, 8.9 Hz), 4.65 (AB pattern, 2H, J=12.1 Hz, $\Delta\nu$=53.4), 5.68 (d, 1H, J= 8.9 Hz), 7.05–7.11 (m, 2H), 7.15–7.23 (m, 2H), 7.27–7.35 (m, 6H). ^{13}C NMR (75 MHz): δ 18.8 (CH_3), 20.0 (CH_3), 28.3 (CH), 47.5 (CH), 48.6 (CH), 67.2 (CH_2), 79.0 (CH), 125.8 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 128.8 (CH), 134.6 (C), 135.7 (C), 169.5 (C=O), 176.7 (C=O). HRMS calcd for $C_{21}H_{23}O_4$ [MH^+]: 339.1596; found: 339.1594.

4.2.23. 3-(4-*i*-Propyl-5-oxo-2-phenyl-tetrahydro-furan-3-carbonyl)-4-isopropyl-oxazolidin-2-one (25). Treating **10** (200 mg, 0.94 mmol) according to method B led to 215 mg of a mixture containing lactones **25** (4 stereoisomers), together with lactones bearing a carbethoxy group (resulting from the transfer of the isopropyl group to the carbon α to the carbonyl bearing the auxiliary), in a 70:30 ratio (rough estimate based on the NMR signals of the protons α to the phenyl group), isolated after purification by FC (5–20%, EtOAc–pentane).

^{1}H NMR (300 MHz) of the major isomer: (**25**): ^{1}H NMR (300 MHz): δ 1.03 (d, 3H, J=7.0 Hz), 1.07 (d, 3H, J=6.8 Hz), 2.31 (m, 1H), 3.12 (ddd, 1H, J=10.9, 9.2, 6.6 Hz), 3.48 (dd, 1H, J=6.8, 5.7 Hz), 3.67–3.79 (m, 1H), 3.98 (dt, 1H, J=7.2, 9.2 Hz), 4.23 (dt, 1H, J=6.6, 9.2 Hz), 4.88 (dd, 1H, J=9.2, 6.8 Hz), 5.83 (d, 1H, J=9.2 Hz), 7.17–7.25 (m, 2H), 7.30–7.37 (m, 3H). ^{13}C NMR (75 MHz): δ 19.0 (CH_3), 20.1 (CH_3), 28.8 (CH), 42.4 (CH_2), 47.2 (CH), 47.3 (CH), 62.1 (CH2), 79.3 (CH), 126.2 (CH), 128.4 (CH), 129.0 (CH), 135.9 (C), 153.1 (C=O), 169.5 (C=O), 177.0 (C=O). HRMS calcd for C17H19NO5Na [MNa+]: 340.1161; found: 340.1157.

4.2.24. (2*R-3*S**-4*S**) 4-*i*-Propyl-5-oxo-2-phenyl-tetrahydro-furan-3-carboxylic acid (*rac*-21).** H_2O_2 (30%) (266 μL, 2.60 mmol) and LiOH.H_2O (41 mg, 0.98 mmol) were added at 0 °C to a solution of the preceding mixture of lactones (206 mg, 0.65 mmol) in THF (4.3 mL) and H_2O (1.1 mL). The mixture was stirred for 1 h at 0 °C. After completion, the excess of H_2O_2 was reduced by addition of an aqueous solution of NaS_2O_3 (10%). THF was removed under reduce pressure at room temperature. The residual aqueous solution (pH=12) was then extracted with EtOAc (×3). The aqueous phase was then acidified with HCl (10%) up to pH=1 and extracted with EtOAc (×5). The extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduce pressure to give racemic **21** as a white solid (131 mg).

4.2.25. (2*R-3*S**-4*S**)4-*i*-Propyl-5-oxo-2-phenyl-tetrahydro-furan-3-carboxylic acid benzyl ester (*rac*-22).** A mixture of *rac*-**21** (131 mg, 0.53 mmol, 1 equiv), benzyl bromide (122 μL, 1.03 mmol, 2 equiv) and DBU (118 μL, 0.79 mmol, 1.5 equiv) in benzene (1.8 mL) was stirred at 60 °C for 2 h. After cooling to room temperature, insoluble materials were filtered off. The filtrate was concentrated under reduce pressure. The residue was purified on silica gel (10% EtOAc–pentane) to give racemic **22** (105 mg, 0.31 mmol, 58%) of as a 90:6:4 mixture of diastereomers. The spectral data were identical to those already described for the optically active compound.

4.2.26. 2-*i*-Propyl-1,4-bis-((*S*)-4-*i*-propyl-2-oxo-oxazolidin-3-yl)-butane-1,4-dione (13f,g). Zn(*i*-Pr)$_2$ (266 μL, 0.266 mmol, 2 equiv) was added to a solution of **1** (45 mg, 0.133 mmol) in dichloromethane (650 μL). The reaction was stirred at −10 °C while air was injected in the solution. After completion the reaction was quenched with aqueous NH_4Cl, and the aqueous phase was extracted with CH_2Cl_2 (×3). The combined organic layers were dried over anhydrous Na_2SO_4 and then concentrated. The crude product was purified by semi-preparative chromatography (CHIRALCEL OD (250×10 mm), hexane–ethanol (90:10), 4.5 mL/min, UV detection at 220 nm). This led, by order of elution, to **13g** (8.21 min, 3.9 mg, 8%), **13h** (9.12 min, 14.1 mg, 28%), **13f** (10.46 min, 11.7 mg, 23%).

Compound **13f**. Mp 144–145 °C. ^{1}H NMR (300 MHz): δ 0.86 (d, 3H, J=6.8 Hz), 0.87 (d, 3H, J=7.0 Hz), 0.91 (d, 3H, J=7.0 Hz), 0.95 (d, 6H, J=7.0 Hz), 1.01 (d, 3H, J=6.8 Hz), 1.99 (pseudo oct, 1H, J=6.8 Hz), 2.23 (dsept, 1H, J=4.3, 6.8 Hz), 2.37 (dsept, 1H, J=3.8, 7.0 Hz), 3.13 (dd, 1H, J=3.0, 18.3 Hz), 3.46 (dd, 1H, J=11.9, 18.3 Hz), 4.16–4.31 (m, 5H), 4.35–4.45 (m, 2H). ^{13}C NMR (75 MHz): δ 14.5 (CH_3), 15.1 (CH_3), 17.8 (CH_3), 18.0 (CH_3), 18.5 (CH_3), 20.6 (CH_3), 28.1 (CH), 28.7 (CH), 29.8 (CH), 34.9 (CH_2), 43.8 (CH), 58.4 (CH), 58.9 (CH), 62.9 (CH_2), 63.9 (CH_2), 153.8 (C=O), 154.1 (C=O), 172.3 (C=O), 175.4 (C=O). HRMS calcd for $C_{19}H_{30}N_2O_6Na$ [MNa^+]: 405.2002; found: 405.2003.

Compound **13g**. ^{1}H NMR (300 MHz): δ 0.86 (d, 3H, J=7.0 Hz), 0.88 (d, 3H, J=7.0 Hz), 0.89 (d, 3H, J=7.0 Hz), 0.92 (d, 3H, J=7.0 Hz), 0.94 (d, 3H, J=7.0 Hz), 1.08 (d, 3H, J=7.0 Hz), 2.09–2.20 (m, 1H), 2.25–2.40 (m, 2H), 3.08 (dd, 1H, J=3.0, 18.5 Hz), 3.42 (dd, 1H, J=11.7, 18.7 Hz), 4.12–4.36 (m, 6H), 4.42–4.50 (m, 1H). ^{13}C NMR (75 MHz): δ 14.5 (CH_3), 14.7 (CH_3), 18.0 (2×CH_3), 18.1 (CH_3), 20.8 (CH_3), 28.3 (CH), 28.7 (CH), 29.9 (CH), 33.7 (CH_2), 43.7 (CH), 58.4 (CH), 58.5 (CH), 63.2 (CH_2), 63.4 (CH_2), 153.9 (C=O), 154.0 (C=O), 172.3 (C=O), 175.5 (C=O). HRMS calcd for $C_{19}H_{31}N_2O_6$ [MH^+]: 383.2182; found: 383.2196.

4.2.27. (*S*)-3-((*S*)-1-Hydroxymethyl-2-methyl-propyl)-5-*i*-propyl-7-((*S*)-4-*i*-propyl-2-oxo-oxazolidin-3-yl)-5*H*-[1,3]-oxazepine-2,4-dione (13h). ^{1}H NMR (300 MHz): δ 0.82 (d, 3H, J=6.8 Hz), 0.90 (d, 3H, J=7.0 Hz), 0.94 (d, 3H, J=7.0 Hz), 0.96 (d, 3H, J=6.5 Hz), 1.01 (d, 3H, J=6.8 Hz), 1.02 (d, 3H, J=6.8 Hz), 2.29–2.51 (m, 3H), 3.34 (pseudo t, 1H, J=5.1 Hz), 3.75–3.88 (m, 2H), 4.03 (m, 1H), 4.28 (dd, 1H, J=8.9, 2.5 Hz), 4.39 (pseudo t, 1H, J=8.5 Hz), 4.49 (ddd, 1H, J=7.9, 3.8, 2.5 Hz), 5.45 (br s, 1H). ^{13}C NMR (75 MHz): δ 14.8 (CH_3), 17.7 (CH_3), 17.9 (CH_3), 19.6 (CH_3), 19.8 (CH_3), 20.1 (CH_3), 26.1 (CH), 27.8 (CH), 28.7 (CH), 45.0 (=CH), 50.53 (CH), 59.3 (CH), 61.2 (CH), 61.4 (CH_2), 63.8 (CH_2), 153.9 (C=O), 167.9 (C=), 173.6 (C=O), 178.7 (C=O). HRMS calcd for $C_{19}H_{31}N_2O_6$ [MH^+]: 383.2182; found: 383.2181.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.02.042.

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15. According to Table 1, it can be noted that the carbonyl group bearing the auxiliary induces a deshielding of the *cis* protons. The deshielding effect is significant on H4 (0.20–0.23 ppm (cf. **3**,**5/7**), or 0.40–0.53 ppm (cf **19/20** or **15/17**)), it is negligible on H2. H3 is shielded by 0.34–0.67 ppm by the *syn* alkyl group (cf. **3**,**5/4**,**6** or **15**,**19/16**,**18**), it suffers a larger shielding effect from the *syn* phenyl group (1.03–1.08 ppm, (cf. **7/4**,**6**) or 0.83–1.11 ppm, (cf. **17**,**20/16**,**18**)).
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17. The cleavage of a pure sample of **5**, later obtained from substrate **2**, confirmed that **5** did not lead to acid **8**, but to a mixture of products containing another amide-alcohol **12b**.
18. The reaction conducted with 10 equivalents of *t*-BuI gave also a clear evidence for the competition between the addition of *t*-Bu$^{\cdot}$ and Et$^{\cdot}$.
19. The diastereomeric ratio was roughly estimated by ^{1}H NMR from the integration of the overlapping AB parts of the ABX systems in each diastereomer.
20. The tridimensional structure of **5** clearly reveals that both faces of the exocyclic carbonyl group are hindered and none can be attacked by the nucleophile.
21. All seven lactones exhibited characteristic doublets for the proton α to the phenyl group at: 6.03 ppm (J=9.1 Hz), 16%; 5.86 ppm (J=7.5 Hz), 16%; 5.84 ppm (J=7.4 Hz), 24%; 5.83 ppm (J=8.9 Hz), 5%; 5.69 ppm (J=5.7 Hz), 28%; 5.63 ppm (J=5.9 Hz), 5%; 5.44 ppm (J=9.1 Hz). The relative ratio were grossly estimated from the ^{1}H NMR spectrum of the mixture after elimination of unreacted benzaldehyde by liquid chromatography.
22. The racemic lactone **25** was prepared via the addition of *i*-Pr$^{\cdot}$ to **10**. The addition of Zn(*i*-Pr)$_2$ to **10** in the presence of benzaldehyde led to a mixture of regioisomers (26% of isomeric lactones resulted from the attack of *i*-Pr$^{\cdot}$ at the vinylic carbon α to the carbonyl bearing the auxiliary). The saponification led to the crude acid in 81% yield. The corresponding benzylic ester was isolated in 59% overall yield as a mixture of 3 quantifiable diastereomers (dr=90:6:4). The major isomer showed ^{1}H NMR signals very close to those of **9** (cf. Table 1).
23. It must be noted that in the NMR spectra of **13h** (and **13c**) and to a lesser extent the spectrum of **13d**, the doublet corresponding to the vinylic proton and the signal of the corresponding carbon are broadened. This phenomenon is probably related to the rate of rotation around the C–N bond. Lowering the temperature at -10 °C afforded well resolved spectra and allowed to unambiguously establish the correlation between the protons and the corresponding carbons by HMQC.
24. The relative ratio of **15**–**20** and **23** was determined both from the ^{1}H NMR spectrum of the mixture and from the chromatographic separation: **15** (6.5%), **17** (30%), **16** (7%),

23 (6.5%), **18** (11%), **19** (33%), **20** (6%). The characteristic ^{1}H and ^{13}C NMR signals of **23** could be determined from an isolated mixture of **23** and **16**. **23** might have a *trans*, *trans* relative configuration according to the coupling constants ($J_{23}=9.4$, $J_{34}=10.9$ Hz) very similar to those reported by Sibi in Ref. 9 for nephrosteranic acid ($J_{23}=9.4$ Hz, $J_{34}=11.3$ Hz) and roccelaric acid ($J_{23}=9.4$ Hz, $J_{34}=11.4$ Hz).

25. The ^{1}H NMR spectrum of enriched chromatographic fractions clearly show the characteristic signals of the ethoxycarbonyl groups and the absence of the oxazolidinone protons (cf. Section 4.2.20).
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27. Supporting Information content: Chiral HPLC analyses of racemic and optically pure lactones **9** and **22** (S2–S5), of lactones **15**, **16**, **17**, **18**, **19** and **20** (S6), detailed chiral HPLC conditions (S7). Significant NOESY correlations for lactones **9** and **15**–**20** (S8).
28. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 257463 for lactone **3**, 257464 for lactone **4**, 257465 for lactone **5**, and 257466 for lactone **18**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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Ferric chloride/tetraethyl orthosilicate as an efficient system for synthesis of dihydropyrimidinones by Biginelli reaction

Ivica Cepanec,* Mladen Litvić, Anamarija Bartolinčić and Marija Lovrić

BELUPO Pharmaceuticals, Research Department, Radnička c. 224, 10000 Zagreb, Croatia

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Abstract—An efficient method for the Biginelli reaction of aldehydes, acetoacetate esters and urea employing tetraethyl orthosilicate in the presence of ferric chloride is described. These improved reaction conditions allow the preparation of a wide variety of substituted dihydropyrimidinones (including sterically encumbered ones) in high yields and purity under mild reaction conditions.

1. Introduction

The Biginelli reaction[1] is a well-known, simple and straightforward procedure for the synthesis of dihydropyrimidinones by the three-component condensation of aliphatic or aromatic aldehyde, acetoacetate ester and urea. Since dihydropyrimidinones exhibit significant biological activity (e.g. as calcium channel blockers), their synthesis has been the focus of much interest from organic and medicinal chemists.[2] In its original version, the reaction is conducted in boiling ethanol in the presence of catalytic amounts of concentrated aqueous hydrochloric acid. This simple procedure has been effective in a number of the Biginelli reactions with simple unsubstituted, or *para*- and *meta*-substituted aldehydes and acetoacetate esters.[3–9] However, in cases of significant steric hindrance in both counterparts the reaction yields drop drastically. In order to improve the yield of dihydropyrimidinones, a few other multistep approaches using aldehyde[10] or acetoacetate[11] equivalents in modified Biginelli reactions have been developed. Nevertheless, the original Biginelli reaction offers the most simple, cost-effective and reasonable access to these important compounds.

During the last decade, several efficient methods based on metal-catalysed Biginelli reaction have been reported. Among the simple metal (and ammonium) salts with nucleophilic anions, e.g. LiBr,[12] NH_4Cl,[13] $NiCl_2 \cdot 6H_2O$,[14] $FeCl_3 \cdot 6H_2O$,[14] $CuCl_2 \cdot 2H_2O$,[15] $CeCl_3 \cdot 7H_2O$,[16] $Mn(OAc)_3 \cdot 2H_2O$,[17] $ZrCl_4$,[18] $InCl_3$,[19] $InBr_3$,[20] $ZnCl_2$,[21] ZnI_2,[22] $CdCl_2$,[23] $BiCl_3$[24] are active catalysts. The catalytic effect of metal cations is even more pronounced with methods based on metal salts with non-nucleophilic anions such as $LiClO_4$,[25] $CuSO_4 \cdot 5H_2O$,[15] $Zn(OTf)_2$,[26] $Cu(OTf)_2$,[27] $Al(HSO_4)_3$,[28] $BiONO_3$,[29] or variuos lanthanide triflates, $Ln(OTf)_3$ (Ln = Yb, Sc, La).[30–32] The most efficient catalysts are bismuth triflate[33,34] and trimethylsilyl triflate,[35] which allow the preparation of dihydropyrimidinones in good to high yields at room temperature. Another effective Biginelli reaction conditions employing stoichiometric reagents are $BF_3 \cdot Et_2O$ and catalytic AcOH/CuCl in refluxing THF,[36] $(CH_3)_3SiCl$ (TMSCl),[37] TMSCl/NaI,[38] or TMSCl/DMFA.[39] Additionally, the Biginelli reaction can be strongly accelerated by various ionic liquids in catalytic amounts, e.g. 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ($BMImBF_4$).[40] Finally the reaction can be performed by simple heating a neat mixture of aldehyde, acetoacetate and urea (in slight excess) at 100–105 °C under solventless conditions for a few hours with fair yields.[41]

Although many of the above mentioned methods give pure dihydropyrimidinone in good to excellent yields, in almost all cases the model compounds were selected from simple acetoacetate esters, either methyl or ethyl acetoacetate, and, mainly, *meta*- and *para*-substituted aromatic aldehydes with no significant steric demands. As a consequence, many of these methods do not work with sterically encumbered Biginelli counterparts.

In contrast to simple catalytic methods, those employing suitable dehydrating agents have proved more effective, even in the cases of more complicated dihydropyrimidinones. Thus, Kappe and coworkers[42] described a simple, effective and general method for Biginelli reaction based on

Keywords: Biginelli reaction; Dihydropyrimidinones; Ferric chloride; Tetraethyl orthosilicate.
* Corresponding author. Fax: +385 1 2408 074;
e-mail: ivica.cepanec@belupo.hr

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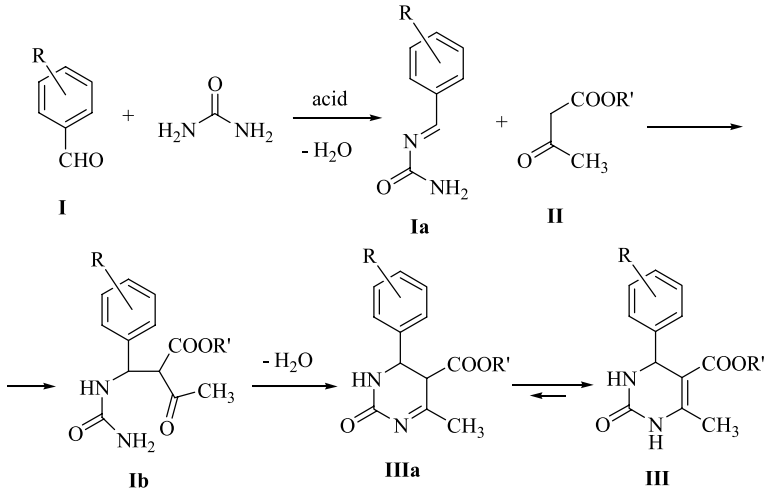
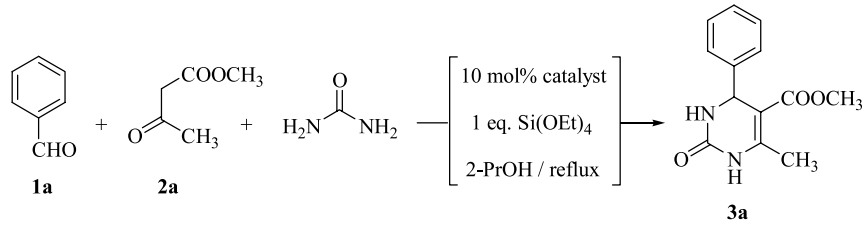


Scheme 1.



Scheme 2.

ethyl polyphosphate (PPE) mediated reaction under quite mild reaction conditions (refluxing THF). Moreover, it has been found that the procedure can be further speeded-up using microwave heating.[43] Except the work from Kappe's group, not much attention has been paid to the synthetic methods applicable to all kinds of dihydropyrimidinones, including the sterically hindered ones.

We decided to study the Biginelli reaction based on tetraethyl orthosilicate ($Si(OEt)_4$) in the presence of a suitable acid catalyst. $Si(OEt)_4$ is an extremely efficient reagent in the synthesis of sterically encumbered Schiff's bases.[44] Since the generally accepted Biginelli reaction mechanism[45–47] (Scheme 1) involves the formation of C═N bond from the parent aldehyde (**I**) and urea followed by (protic or Lewis) acid-catalysed addition of acetoacetate ester (**II**) to the protonated aryl(or alkyl)idene–urea (**Ia**) and cyclodehydration (via **Ib**) yielding dihydropyrimidinones (**III**), $Si(OEt)_4$ might promote the reaction by accelerating the formation C═N bond (rate-determining step).

The same effect was successfully employed in the synthesis of 1,4-dihydropyridines, where $Si(OEt)_4$ dramatically accelerates the acid-catalysed Hantzsch condensation of aldehyde, acetoacetate ester and ammonium acetate furnishing very pure 1,4-dihydropyridines in excellent yields.[48]

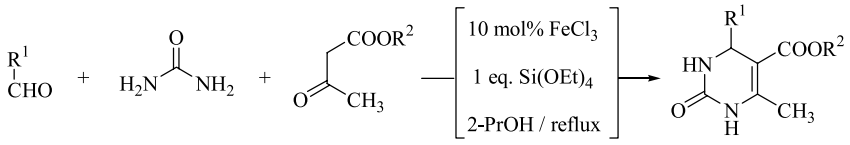
2. Results and discussion

First, we examined the effect of various Lewis acids and 10 mol % $PhSO_3H$ on the model reaction of benzaldehyde (**1a**, 1 equiv), methyl acetoacetate (**2a**, 1.05 equiv), and urea (1.2 equiv) in the presence of $Si(OEt)_4$ (1 equiv) affording 5-methoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (**3a**) in various yields (Scheme 2). Since the model reaction catalysed by $PhSO_3H$ performed in refluxing acetonitrile (80 °C) or THF (65 °C) gave significantly lower yields than in isopropanol, all other reactions in this study were conducted in the latter reaction solvent. The results are presented in Table 1.

Table 1. Catalyst effect in the model Biginelli reaction (Scheme 2)

Entry	Catalyst (10 mol%)	Time (h)[a]	Yield (%)[b]
1	–	24	8
2[c]	37% HCl aq.	5	47
3	$PhSO_3H$	4	59 (51,[d] 43[e])
4	$NiCl_2$	20	72
5	$CeCl_3$	20	65
6	$ZnCl_2$	20	52
7	$AlCl_3$	20	64
8	$CuCl_2$	4	71
9	$Cu(OTf)_2$	4	75
10	$Fe(OAc)_2$	24	41
11	$FeCl_3$	2.5	88
12	$FeCl_3$[f]	4	94

[a] The reactions were monitored by TLC until the disappearance of starting methyl acetoacetate (**2a**).
[b] Yields of isolated and recrystallised product (from 96% EtOH).
[c] This reaction was carried out in refluxing 96% EtOH, representing the classical Biginelli conditions.
[d] In refluxing MeCN.
[e] In refluxing THF.
[f] Methyl acetoacetate (**2a**) was added dropwise to the reaction mixture at reflux temperature during 2 h, plus 2 h additional heating.



1a: R^1= Ph

1b: R^1= 2-$O_2NC_6H_4$

1c: R^1= 4-$O_2NC_6H_4$

1d: R^1= 2-$CH_3OC_6H_4$

1e: R^1= 4-$CH_3OC_6H_4$

1f: 1-naphthyl

1g: 1-anthryl

1h: 2-Pr

1i: PhCH=CH

2a: R^2= Me

2b: R^2= Et

2c: R^2= 2-Pr

2d: R^2= *i*-Bu

2e: R^2= Bn

3a: R^1= Ph, R^2= Me

3b: R^1= Ph, R^2= Et

3c: R^1= Ph, R^2= 2-Pr

3d: R^1= Ph, R^2= *i*-Bu

3e: R^1= Ph, R^2= Bn

3f: R^1= 2-$O_2NC_6H_4$, R^2= Me

3g: R^1= 4-$O_2NC_6H_4$, R^2= Me

3h: R^1= 2-$CH_3OC_6H_4$, R^2= Me

3i: R^1= 4-$CH_3OC_6H_4$, R^2= Me

3j: R^1= 1-naphthyl, R^2= Me

3k: R^1= 1-anthryl, R^2= Me

3l: R^1= 2-Pr, R^2= Me

3m: R^1= PhCH=CH, R^2= Et

Scheme 3.

The Biginelli reaction in the presence of $Si(OEt)_4$ is actually catalysed by all catalysts probed but with significant differences in their activity. Although $Cu(OTf)_2$ and $CuCl_2$ (entries 8 and 9) were quite effective catalysts, anhydrous $FeCl_3$ was selected as the most efficient. As one could predict, the decreased yields in the Biginelli condensation is caused mainly due to acetoacetate ester polymerisation prior to reaction with urea–aldehyde adduct (Biginelli reaction pathway). To overcome this side-reaction, methyl acetoacetate (**2a**) was added dropwise to the refluxing reaction mixture of urea, benzaldehyde, $Si(OEt)_4$ and $FeCl_3$ (10 mol %). Employing this reverse-mode of reactant addition, a significant further improvement of the reaction yield was achieved (entry 12).

This method was further studied in several model Biginelli reactions of various aromatic (**1a–g**) or aliphatic (**1h**) aldehydes, and trans-cinnamaldehyde (**1i**) as α,β-unsaturated aldehyde with acetoacetate esters (**2a–e**) and urea to give the respective dihydropyrimidinones (**3a–m**) in good to high yields (Scheme 3). As the reaction proceeds, the silica gel precipitates from the reaction mixture indicating the progress of the Biginelli reaction. The results are presented in Table 2.

Table 2. Synthesis of dihydropyrimidinones **3a–m** by anhydrous $FeCl_3$-catalysed Biginelli reaction in the presence of $Si(OEt)_4$

Entry	Product	R^1	R^2	Time (h)[a]	Yield (%)[b]
1	**3a**	Ph	Me	2.5	94
2	**3b**	Ph	Et	3	88
3	**3c**	Ph	2-Pr	3	85
4	**3d**	Ph	*i*-Bu	4	92
5	**3e**	Ph	Bn	6 (4[c])	79 (86[c])
6	**3f**	2-$O_2NC_6H_4$	Me	10	81
7	**3g**	4-$O_2NC_6H_4$	Me	4	86
8	**3h**	2-$CH_3OC_6H_4$	Me	4 (3[d])	73 (88[d])
9	**3i**	4-$CH_3OC_6H_4$	Me	4	92
10	**3j**	1-Naphthyl	Me	4	86
11	**3k**	9-Anthryl	Me	19	95
12	**3l**	2-Pr	Me	3.5	71
13	**3m**	PhCH=CH	Et	2	80

[a] Determined by TLC.
[b] Yields of recrystallised products (0.1 mol scale).
[c] In 2-butanol as reaction solvent.
[d] In cyclohexanol as reaction solvent.

Aromatic aldehydes bearing both electron-donating and electron-withdrawing groups readily undergo the reaction giving fair yields of the corresponding Biginelli compounds. Steric demands of *ortho*-substituted aromatic aldehydes and larger alkyl-moieties in the acetoacetate esters are also well tolerated. The choice of isopropanol (secondary alcohol) as reaction solvent was optimal since the primary alcohols such as methanol, abs. ethanol, or 1-propanol (slightly less) led to the formation of transesterification by-products. For example, when the reaction of methyl acetoacetate (**2a**), benzaldehyde (**1a**) and urea was conducted in refluxing anhydrous ethanol, a mixture of methyl- and ethyl-esters of the respective 1,4-dihydropyrimidinone, **3a** and **3b** was isolated in almost equimolar ratio (determined by ^{1}H NMR spectroscopy). We believe that the transesterification side-products are formed in relatively slower Biginelli reactions by reaction of primary alcohols with the starting acetoacetate ester under the influence of $FeCl_3$ as catalyst, prior to the Biginelli condensation. The reaction of dihydropyrimidinone **3a** in refluxing ethanol in the presence of anhydrous $FeCl_3$ (10 mol %) did not afford the respective compound **3b** at all. This clearly indicates that the transesterification side-products are formed at the acetoacetate-stage. According to our knowledge the $FeCl_3$-catalysed transesterification of acetoacetate esters has not been described so far. This simple and interesting reaction is under investigation and will be published elsewhere. Other secondary alcohols such as 2-butanol or cyclohexanol can be also successfully used as alternative reaction solvents since they give slightly higher yields with sluggish Biginelli reactions, presumably as a result of the higher temperatures that can be used (entries 5 and 8).

3. Conclusion

The Biginelli reaction can be efficiently performed employing tetraethyl orthosilicate as dehydrating agent in refluxing isopropanol in the presence of catalytic amount of anhydrous ferric chloride giving good to high yields of pure dihydropyrimidinones.

4. Experimental

IR spectra were recorded on a Perkin-Elmer Spectrum One spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a AV Bruker (600 MHz) spectrometer, and shifts are given in ppm downfield from TMS as an internal standard. TLC analyses were performed on Merck's (Darmstadt, Germany) DC-alufolien with Kieselgel 60F_{254}. Melting points were determined using a Büchi B-540 instrument.

4.1. Synthesis of dihydropyrimidinones in the presence of $Si(OEt)_4$ and various Lewis acids and $PhSO_3H$

To a solution of benzaldehyde (**1a**, 1.06 g, 0.01 mol), methyl acetoacetate (**2a**, 1.22 g, 0.0105 mol, 1.05 equiv) in 2-PrOH (20 mL) was added urea (0.72 g, 0.012 mol, 1.2 equiv), tetraethyl orthosilicate (2.2 mL, 2.08 g, 0.01 mol, 1 equiv), followed by metal salt: $NiCl_2$, $CeCl_3$, $ZnCl_2$, $AlCl_3$, $CuCl_2$, $Cu(OTf)_2$, $Fe(OAc)_2$ or $FeCl_3$, or $PhSO_3H$ (1 mmol, 10 mol %) at once. The reaction mixture was refluxed with stirring for the time indicated in the Table 1. The reaction mixture was evaporated to dryness. To a residue, 96% ethanol (40 mL) was added, followed by sodium hydroxide (0.40 g, 0.01 mol) and stirred at room temperature for 1 h. Then, concentrated hydrochloric acid (1.1 mL, 0.48 g HCl, 13 mmol, 1.3 equiv to NaOH) was added and the resulting suspension was evaporated to dryness. The solid residue was extracted with boiling ethanol (3×20 mL) followed by (hot) filtration through a celite. Combined filtrates were evaporated to dryness.

The reaction conducted with $PhSO_3H$, and the classical Biginelli reaction with 37% HCl (aq.) performed in refluxing ethanol were only evaporated to dryness.

The crude products were recrystallised from 96% ethanol (6–8 mL) to give pure samples of 5-methoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (**3a**) as white crystals, mps in a range of 206–210 °C, all within the interval of 2 °C (lit. mp 208–210 °C),[25] and results are presented in the Table 1. Analytical results (mp, IR, ^{1}H and ^{13}C NMR) of products were identical to those reported in the literature, and purities according to ^{1}H NMR were generally >97%.

4.2. General procedure for the synthesis of dihydropyrimidinones 3a–m

To a solution of anhydrous ferric chloride (1.62 g, 0.01 mol, 10 mol%) in 2-PrOH (100 mL) was added urea (7.21 g, 0.12 mol, 1.2 equiv), followed by solution of aldehyde **1a–i** (0.1 mol) in 2-PrOH (50 mL) and tetraethyl orthosilicate (22.3 mL, 20.83 g, 0.01 mol, 1 equiv). The reaction mixture was heated with stirring to a reflux temperature. Then, the solution of acetoacetate ester **2a–e** (0.105 mol, 1.05 equiv) in 2-PrOH (50 mL) was added dropwise during 50% of reaction time indicated in Table 2. Then the heating was continued for the same additional period of time. The reaction mixture was evaporated to dryness. To a residue, 96% ethanol (400 mL) was added, followed by sodium hydroxide (4.00 g, 0.1 mol) and stirred at room temperature for 1 h. Then, concentrated hydrochloric acid (11 mL, 4.82 g HCl, 0.13 mol, 1.3 equiv to NaOH) was added and the resulting suspension was evaporated to dryness. The solid residue was extracted with boiling ethanol (3× 200 mL) followed by (hot) filtration through a celite. Combined filtrates were evaporated to dryness. The crude products were recrystallised from 96% ethanol to give reasonably pure dihydropyrimidinones **3a–m** whose purities, according to ^{1}H NMR, were generally >97%. Analytical results (mp, IR, ^{1}H and ^{13}C NMR) of products **3a**,[25] **3b**,[25] **3f**,[49] **3g**,[20] **3i**,[20] and **3m**[20] were identical to those reported in the literature.

4.2.1. 5-Isopropyloxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (3c). Colourless crystals; mp 189.9–191.2 °C; yield 23.31 g (85%); Found: C, 65.4; H, 6.4; N, 10.1. $C_{15}H_{18}N_2O_3$ requires C, 65.68; H, 6.61; N, 10.21; R_f (10% 2-PrOH/CH_2Cl_2) 0.50; ν_{max} (KBr) 3251, 3120, 2980, 2939, 1722, 1706, 1651, 1468, 1423, 1385, 1348, 1314, 1289, 1227, 1091 cm^{-1}; δ_H (600 MHz, DMSO-d_6) 9.12 (^{1}H NMR, s, N*H*), 7.68 (1H, s, N*H*), 7.30–7.24 (2H, m, arom.), 7.22–7.12 (3H, m, arom.), 5.07

(1H, d, $J=3.2$ Hz, benzylic), 4.77–4.72 (1H, m, C*H*Me$_2$), 2.18 (3H, s, CH_3), 1.09 (3H, d, $J=6.2$ Hz, CH(CH_3)$_2$), 0.91 (3H, d, $J=6.2$ Hz, CH(CH_3)$_2$); δ_C (600 MHz, DMSO-d_6) 164.8, 152.1, 148.1, 145.0, 128.3, 127.2, 126.3, 99.6, 66.3, 54.1, 21.8, 21.4, 17.7.

4.2.2. 5-Isobutyloxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (3d). Colourless crystals; mp 143.7–145.8 °C; yield 26.52 g (92%); Found: C, 66.5; H, 7.0; N, 9.6. $C_{16}H_{20}N_2O_3$ requires C, 66.65; H, 6.99; N, 9.72; R_f (10% 2-PrOH/CH_2Cl_2) 0.53; ν_{max} (KBr) 3254, 3121, 2963, 1721, 1707, 1682, 1648, 1464, 1421, 1393, 1378, 1342, 1314, 1291, 1268, 1223, 1099 cm^{-1}; δ_H (600 MHz, DMSO-d_6) 9.17 (1H, s, N*H*), 7.69 (1H, s, N*H*), 7.31–7.23 (2H, m, arom.), 7.22–7.13 (3H, m, arom.), 5.14–5.05 (1H, m, benzylic), 3.73–3.60 (2H, m, CO_2CH_2-CHMe$_2$), 2.22 (3H, s, CH_3), 1.73–1.65 (1H, m, CO_2CH_2-C*H*Me$_2$), 0.75–0.62 (6H, m, $CO_2CH_2CH(CH_3)_2$); δ_C (600 MHz, DMSO-d_6) 165.3, 152.0, 148.7, 144.6, 128.4, 127.2, 126.2, 99.0, 69.2, 54.0, 27.2, 18.8, 17.8.

4.2.3. 5-Benzyloxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (3e). Colourless crystals; mp 169.1–171.1 °C; yield 25.47 g (79%) in 2-PrOH, and 27.72 g (86%) in cyclohexanol; Found: C, 70.6; H, 5.6; N, 8.5. $C_{19}H_{18}N_2O_3$ requires C, 70.79; H, 5.63; N, 8.69; R_f (10% 2-PrOH/CH_2Cl_2) 0.58; ν_{max} (KBr) 3357, 3219, 3115, 3028, 2978, 2950, 1704, 1687, 1637, 1495, 1455, 1423, 1378, 1321, 1294, 1265, 1223, 1176, 1138, 1105, 1084, 1026 cm^{-1}; δ_H (600 MHz, DMSO-d_6) 9.25 (1H, s, N*H*), 7.75 (1H, s, N*H*), 7.36–7.20 (8H, m, arom.), 7.19–7.16 (2H, m, arom.), 5.22 (1H, d, $J=3.3$ Hz, 4-C*H*), 5.09–5.02 (2H, m, benzyls), 2.30 (3H, s, CH_3); δ_C (600 MHz, DMSO-d_6) 165.0, 152.0, 149.2, 144.6, 136.5, 128.4, 128.2, 127.6, 127.5, 127.2, 126.3, 98.8, 64.8, 53.9, 17.8.

4.2.4. 5-Methoxycarbonyl-6-methyl-4-(2-methoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (3h). Colourless crystals; mp 283.3–285.7 °C; yield 20.17 g (73%) in 2-PrOH, and 24.31 g (88%) in 2-BuOH; Found: C, 60.7; H, 5.9; N, 10.0. $C_{14}H_{16}N_2O_4$ requires C, 60.86; H, 5.84; N, 10.14; R_f (10% 2-PrOH/CH_2Cl_2) 0.55; ν_{max} (KBr) 3367, 3263, 3109, 3023, 2964, 2952, 2837, 1700, 1643, 1598, 1589, 1487, 1465, 1436, 1427, 1379, 1337, 1319, 1287, 1275, 1244, 1218, 1184, 1169, 1102, 1084, 1051, 1028 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 9.16 (1H, s, N*H*), 7.27 (s, 1H, N*H*), 7.24–7.21 (1H, m, arom.), 7.10–6.98 (2H, m, arom.), 7.24–7.21 (1H, m, arom.), 5.51–5.47 (1H, m, benzylic), 3.80 (3H, s, OCH_3), 3.47 (3H, s, COOCH_3), 2.29 (3H, s, CH_3); δ_C (600 MHz, $CDCl_3$) 165.9, 156.6, 152.3, 149.3, 131.2, 128.8, 126.8, 120.2, 111.3, 97.2, 55.4, 50.8, 48.8, 17.8.

4.2.5. 5-Methoxycarbonyl-6-methyl-4-(1-naphthyl)-3,4-dihydropyrimidin-2(1*H*)-one (3j). Colourless crystals; mp 233.8–236.0 °C; yield 25.47 g (86%); Found: C, 68.9; H, 5.3; N, 9.3. $C_{17}H_{16}N_2O_3$ requires C, 68.91; H, 5.44; N, 9.45; R_f (10% 2-PrOH/CH_2Cl_2) 0.57; ν_{max} (KBr) 3363, 3244, 3119, 2951, 1699, 1645, 1603, 1511, 1463, 1427, 1399, 1377, 1320, 1278, 1267, 1231, 1221, 1181, 1140, 1115, 1088, 1036 cm^{-1}; δ_H (600 MHz, DMSO-d_6) 9.35 (1H, s, N*H*), 8.35 (1H, d, $J=8.2$ Hz, N*H*), 7.96 (1H, d, $J=7.6$ Hz, arom.), 7.89–7.84 (2H, m, arom.), 7.63–7.42 (4H, m, arom.), 6.10 (1H, d, $J=2.8$ Hz, benzylic), 3.38 (3H, s, COOCH_3), 2.42 (3H, s, CH_3); δ_C (600 MHz, DMSO-d_6) 165.8, 151.9, 149.2, 139.9, 133.6, 130.1, 128.5, 128.0, 126.2, 125.7, 124.3, 124.0, 123.6, 98.8, 50.7, 49.8, 17.9.

4.2.6. 5-Methoxycarbonyl-6-methyl-4-(9-anthracenyl)-3,4-dihydropyrimidin-2(1*H*)-one (3k). Colourless crystals; mp 250.4–253.1 °C; yield 32.62 g (95%); Found: C, 72.6; H, 4.9; N, 7.9. $C_{21}H_{18}N_2O_3$ requires C, 72.82; H, 5.24; N, 8.09; R_f (10% 2-PrOH/CH_2Cl_2) 0.58; ν_{max} (KBr) 3351, 3228, 3108, 3052, 2948, 1694, 1639, 1526, 1488, 1453, 1430, 1372, 1309, 1234, 1189, 1158, 1143, 1101 cm^{-1}; δ_H (600 MHz, DMSO-d_6) 9.46 (1H, s, N*H*), 8.57 (1H, s, N*H*), 8.51–8.49 (1H, m, arom.), 8.09 (2H, d, $J=8.6$ Hz, arom.), 7.72–7.68 (1H, m, arom.), 7.65–7.47 (4H, m, arom.), 7.04–6.99 (1H, m, arom.), 5.77 (1H, s, benzylic), 2.97 (3H, s, COOCH_3), 2.27 (3H, s, CH_3); δ_C (600 MHz, DMSO-d_6) 166.3, 151.0, 146.5, 135.5, 131.6, 131.5, 129.8, 128.5, 126.2, 125.2, 124.7, 99.9, 50.6, 50.5, 18.2.

4.2.7. 5-Methoxycarbonyl-6-methyl-4-isopropyl-3,4-dihydropyrimidin-2(1*H*)-one (3l). Colourless crystals; mp 211.8–213.9 °C; yield 15.09 g (71%); Found: C, 56.5; H, 7.5; N, 13.2. $C_{10}H_{16}N_2O_3$ requires C, 56.59; H, 7.60; N, 13.20; R_f (10% 2-PrOH/CH_2Cl_2) 0.51; ν_{max} (KBr) 3364, 3240, 3119, 3003, 2955, 2933, 2905, 2873, 1705, 1673, 1650, 1463, 1428, 1381, 1341, 1285, 1233, 1179, 1159, 1135, 1109, 1087 cm^{-1}; δ_H (600 MHz, DMSO-d_6) 8.90 (1H, s, N*H*), 7.27 (1H, s, N*H*), 3.97–3.94 (1H, m, benzylic), 3.59 (3H, s, COOCH_3), 2.17 (3H, s, CH_3), 1.72–1.62 (1H, m, C*H*Me$_2$), 0.81 (3H, d, $J=6.9$ Hz, CH(CH_3)$_2$), 0.73 (3H, d, $J=6.8$ Hz, CH(CH_3)$_2$); δ_C (600 MHz, DMSO-d_6) 166.2, 153.2, 148.6, 98.0, 55.6, 50.6, 34.5, 18.4, 17.7, 15.8.

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Synthesis and biological evaluation of 3-amino-propan-1-ol based poly(ether imine) dendrimers

Thatavarathy Rama Krishna,[a] Samta Jain,[b] Utpal S. Tatu[b,*] and Narayanaswamy Jayaraman[a,*]

[a]*Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012, India*
[b]*Department of Biochemistry, Indian Institute of Science, Bangalore 560012, India*

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Abstract—A general synthetic strategy for the rapid construction of poly(ether imine) dendrons and dendrimers with a nitrogen core, originating from 3-amino-propan-1-ol, is described. A new trifunctional monomer, namely, 3-[bis-(3-hydroxypropyl)amino]propan-1-ol, was used in a divergent synthesis of dendrimers up to the third generation. This method permitted installation of, either alcohol, amine, nitrile, ester or carboxylic acid groups at the peripheries the dendrimers. Cytotoxicity studies on water-soluble carboxylic acid terminated dendrimers were conducted and these studies revealed that poly(ether imine) dendrimers were non-toxic. These results illustrate that poly(ether imine) dendrimers are useful for biological studies.

1. Introduction

Hyperbranched dendritic macromolecules have considerable interest in a number of chemical, biological and materials related studies.[1,2] Dendrimers with biocompatible building blocks has led to the emergence of a new class of dendritic polymers called 'biodendrimers'.[3] Linear polymers such as poly(ethylene glycol) and poly(ethylene imine) are important materials in biological studies[4] and we were interested to combine the molecular features of these two polymers in order to derive new types of biocompatible dendrimers. Herein, we report a facile synthesis of poly(ether imine) dendrons and dendrimers up to the third generation, containing 24 peripheral functionalities, with a nitrogen core, and the evaluation of their cytotoxicity profiles.

2. Results and discussion

2.1. General synthetic methods

For a successful synthesis of dendrimers, high efficiencies and yields of the reactions are essential. In a synthetic strategy, we have identified iterative synthetic sequences involving four reactions, namely, (i) Michael addition to form a nitrile; (ii) reduction of the nitrile to an amine; (iii) double Michael addition of the amine with an acrylate and (iv) reduction of the resulting ester to an alcohol.[5] We herein describe the synthesis, characterization and cytotoxicity of new poly(ether imine) dendrimers with a nitrogen core. The poly(ether imine) (PETIM) dendrimers herein are denoted as PETIM–$m(CO_2R)_n$, PETIM–$m(OH)_n$ PETIM–$m(CN)_n$ and PETIM–$m(CO_2H)_n$, wherein 'm' and 'n' refer to the generation number and the number of terminal groups, respectively.

The iterative reaction sequence was initiated with the Michael addition of acrylonitrile to an alcohol in the presence of aq NaOH. The addition of acrylonitrile to the alcohol has to be carried out slowly, so as not to increase the temperature of the reaction mixture above 30 °C and the reaction was continued for about 6 h. After completion of the reaction, excess acrylonitrile was removed in vacuo, neutralized with aq HCl (1 M) and extracted with $CHCl_3$. Upon a work-up procedure, the required Michael addition product was obtained in excellent yields. Hydrogenation of the nitrile groups with Ra-Co and H_2 (~40 bar) in water/MeOH solvent system afforded the desired primary amine-terminated dendrimers. Subsequent Michael addition of *tert*-butyl acrylate to the amine proceeded readily and the reaction led to almost quantitative yield. Reduction of the *tert*-butyl ester at the peripheries of dendrons and dendrimers to the corresponding alcohols was performed

Keywords: Cytotoxicity; Dendrimers; Michael addition; Raney cobalt.
* Corresponding authors. Tel.: +91 80 2293 2406/2403; fax: +91 80 2360 0529; e-mail: jayaraman@orgchem.iisc.ernet.in

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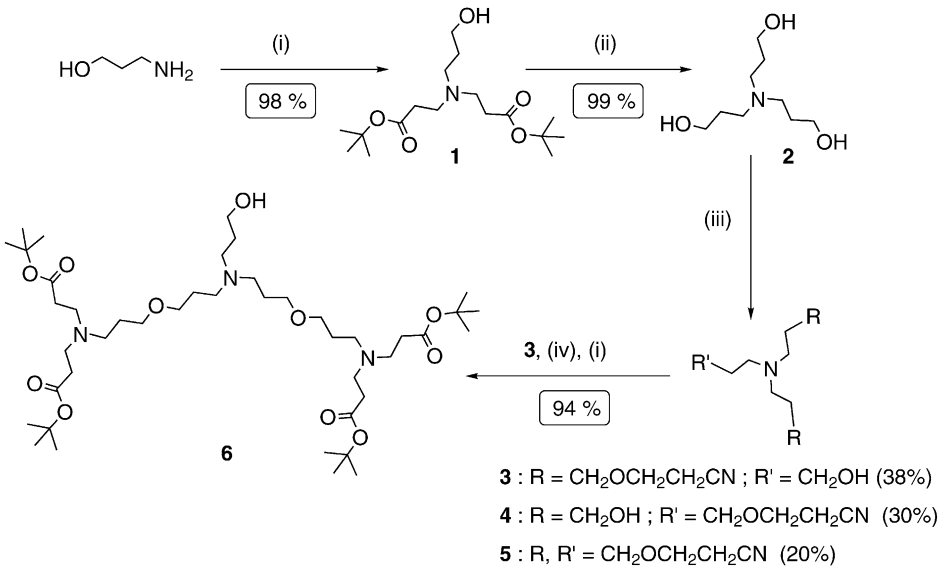
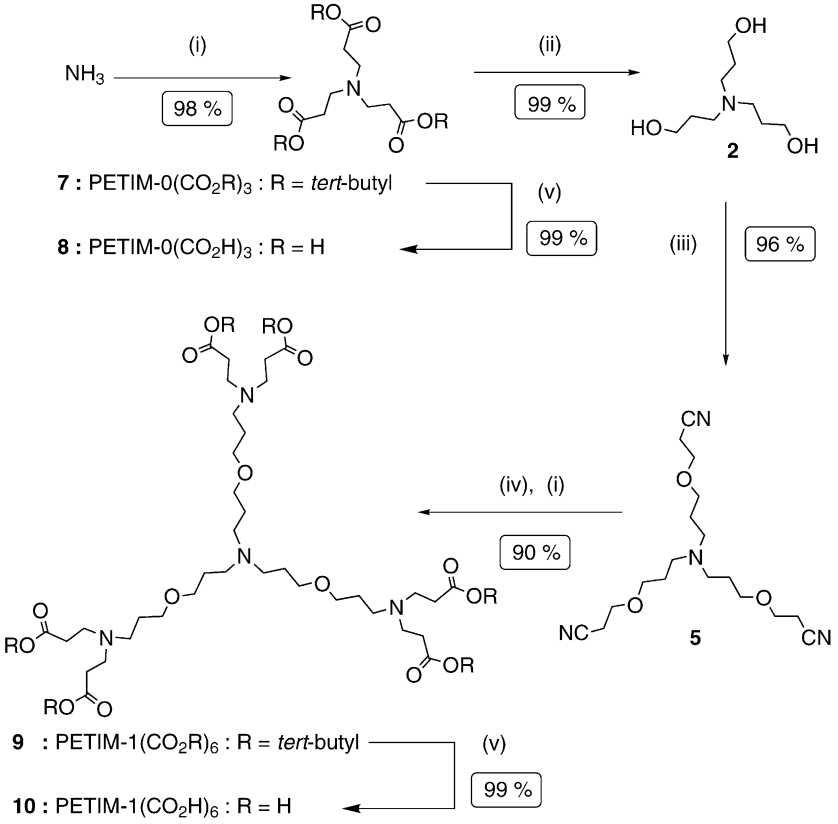


Scheme 1. (i) *tert*-butyl acrylate, MeOH, 6 h; (ii) LAH, THF, 0 °C; (iii) H_2C═CH–CN (2 M equiv), cat. NaOH, 6 h, rt; (iv) Ra-Co, H_2, H_2O/MeOH (99:1), 70 °C, 40 bar.

with LAH in THF and the Michael addition reaction followed, so as to obtain the corresponding nitrile. Although our procedure previously[5] offered a convenient entry to synthesize PETIM dendrons, the present procedure is significantly better, primarily because the synthesis herein is devoid of any protection/deprotection synthetic sequence.

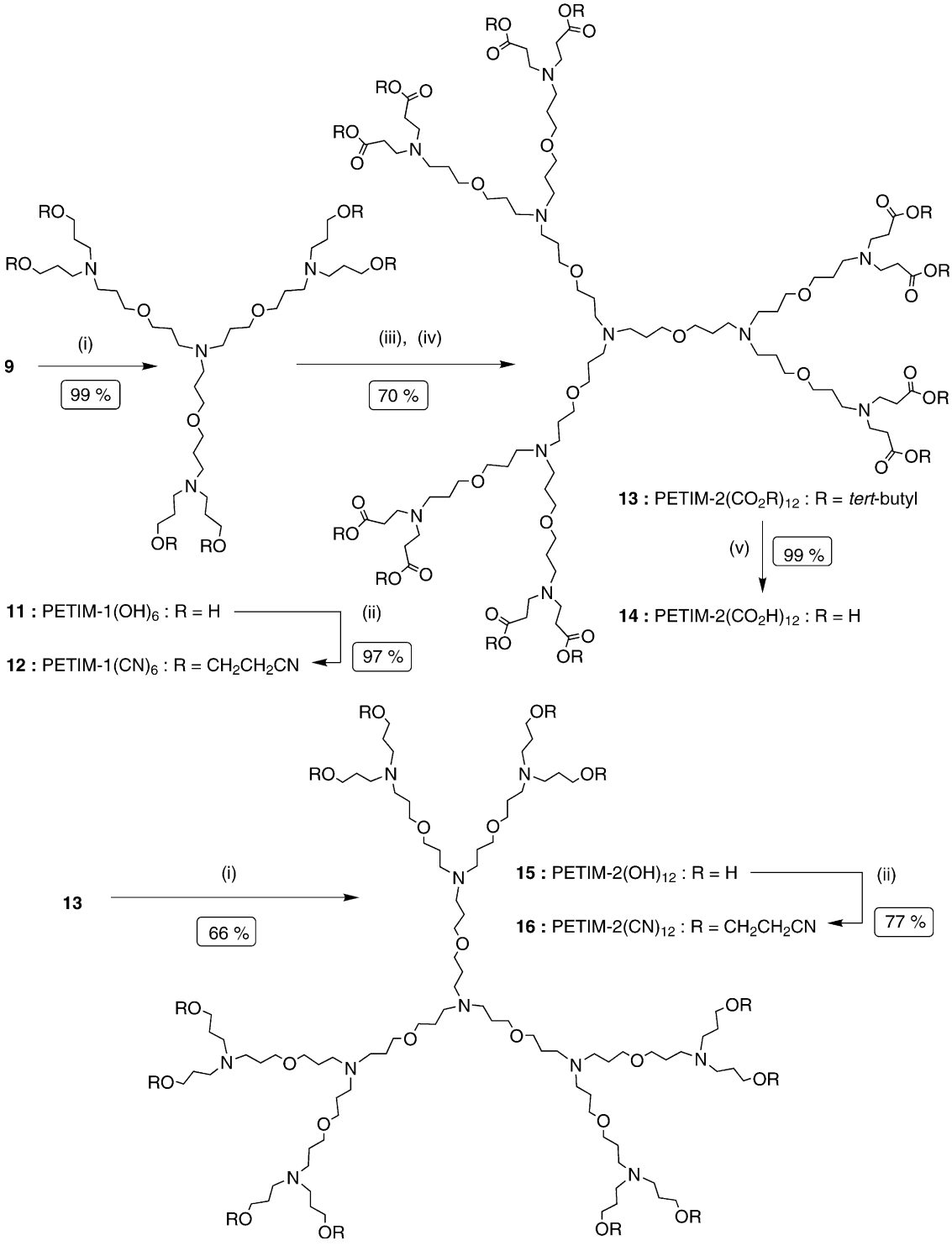
2.2. Synthesis of dendrons

Monomer **1** was synthesized by treatment of 3-amino-propan-1-ol with *tert*-butyl acrylate in quantitative yields (Scheme 1). Reduction of **1** with LAH led to the isolation of 3-[bis-(3-hydroxypropyl)amino]propan-1-ol (**2**), after



Scheme 2. (i) *tert*-butyl acrylate, MeOH, 6 h; (ii) LAH, THF, 0 °C; (iii) H_2C═CH–CN, cat. NaOH, 6 h, rt; (iv) Ra-Co, H_2, H_2O/MeOH (99:1), 70 °C, 40 bar; (v) AcCl, H_2O, CH_2Cl_2, 6 h, rt.

quenching the reaction mixture with ice. Alcohol **2** was subjected to Michael addition to afford bis-nitrile **3**. Apart from **3**, mono-nitrile **4** and tris-nitrile **5** were also obtained. ^{1}H NMR spectrum of mono-, bis- and tris-nitrile exhibited resonances at ~3.63 and ~3.54 ppm corresponding to CH_2CN and OCH_2 protons, respectively. Mono-, bis- and tris-nitriles were identified by comparison of the intensities of the chemical shifts of CH_2CN and OCH_2 protons. The ratio was 1:4 for mono-nitrile **4**; 2:5 for bis-nitrile **3** and 1:2 for tris-nitrile **5**. Bis-nitrile **3** was separated from the mixture of tris- and mono-nitrile product (alumina, $CHCl_3$/MeOH). Reduction of the nitrile groups in **3** with Ra-Co, followed by double Michael addition with tert-butyl acrylate, afforded the second-generation dendron **6** with a free hydroxyl group at the focal point in excellent yields.



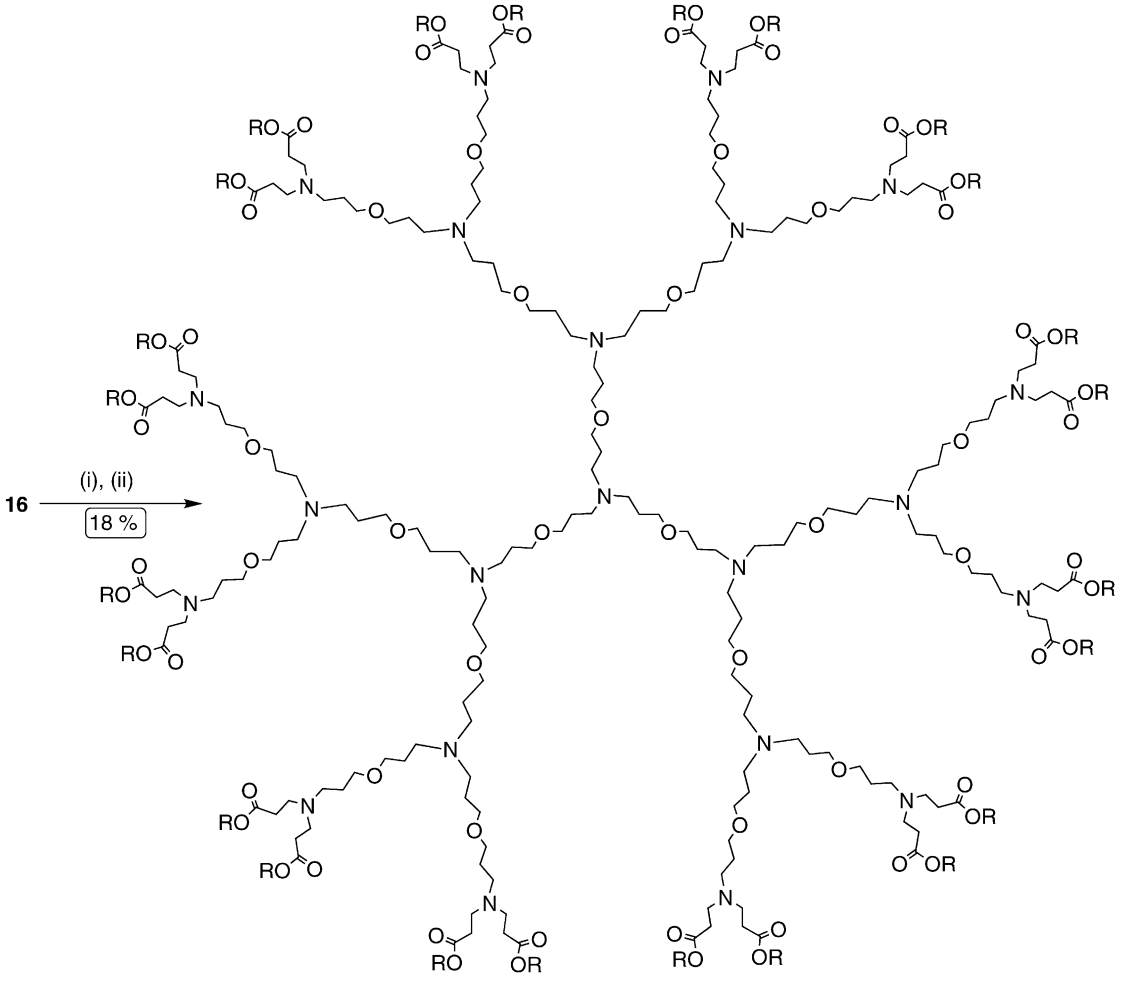
Scheme 3. (i) LAH, THF, 0 °C; (ii) H_2C═CH–CN, cat. NaOH, 6 h, rt; (iii) Ra-Co, H_2, H_2O/MeOH (99:1), 72 °C, 40 bar; (iv) *tert*-butyl acrylate, MeOH, 6 h; (v) AcCl, H_2O, CH_2Cl_2, 6 h, rt.

2.3. Synthesis of dendrimers

An alternative strategy was undertaken in order to synthesize PETIM dendrimers in which the nitrogen atom was the core. The required starting material, ester **7**, was obtained upon treatment of NH_3 with *tert*-butyl acrylate in MeOH (Scheme 2).[6] Reduction of **7** to 3-[bis-(3-hydroxypropyl)amino]-propan-1-ol (**2**) was carried out with LAH in quantitative yields. Treatment of **2** with acrylonitrile afforded tris-nitrile **5** in excellent yields. Hydrogenation of nitrile **5** in a high-pressure autoclave resulted in amine, which was treated with excess *tert*-butyl acrylate, so as to afford PETIM–1$(CO_2R)_6$ (**9**). Ester **9** was subjected to sequential reactions: (i) reduction with LAH to afford PETIM–1$(OH)_6$ (**11**) and (ii) treatment of **11** with acrylonitrile to afford PETIM–1$(CN)_6$ (**12**). Reduction of **12** to an intermediate amine, followed by treatment with *tert*-butyl acrylate afforded PETIM–2$(CO_2R)_{12}$ (**13**) in overall good yields (Scheme 3). An iterative synthetic sequence of Michael addition and reduction reactions was continued with PETIM–2$(CO_2R)_{12}$ (**13**), so as to obtain PETIM–2$(OH)_{12}$ (**15**), which was then treated with acrylonitrile to afford PETIM–2$(CN)_{12}$ (**16**). The nitrile groups in **16** were reduced (Ra-Co, H_2) and the resulting crude amine was subjected to Michael addition with *tert*-butyl acrylate to afford PETIM–3$(CO_2R)_{24}$ (**17**), with 24 ester groups at the periphery of the dendrimer (Scheme 4). In order to generate CO_2H groups at the periphery of dendrimers, the *tert*-butyl ester protecting groups in dendrimers **7**, **9**, **13** and **17** were deprotected (acetyl chloride, H_2O) to afford the free carboxylic acid-containing dendrimers **8**, **10**, **14** and **18**, respectively, in excellent yields.

2.4. Characterization

Characterization of the divergently grown dendrons and dendrimers and their intermediates was performed by spectroscopic and spectrometric techniques. Functional group conversion to nitrile (ν 2251), amine (ν 3460), *tert*-butyl ester (ν 1727) and alcohol (ν 3390) were followed by IR spectroscopy. In ^{1}H NMR spectroscopy, separate resonances were observed for different types of protons, which helped in assigning the structure and constitution of



Scheme 4. Reagents and conditions: (i) Ra-Co, H_2, H_2O/MeOH (99:1), 72 °C, 40 bar; (ii) *tert*-butyl acrylate, MeOH, 6 h; (iii) AcCl, H_2O, CH_2Cl_2, 6 h, rt.

dendrons and dendrimers. Characteristic triplet of protons at ~3.60 ppm for CH_2CN, ~2.30 for CH_2–CO_2 ^tBu, ~1.70 and 3.70 ppm for CH_2CH_2OH were used to check the completion of the reaction and growth of symmetrical dendrimers. ^{13}C NMR chemical shifts could also be used to monitor the functional group transformation at the periphery of dendrons and dendrimers. Specifically, the appearance of chemical shifts for nitrile group at ~117 ppm, carbonyl at ~172 ppm and ~62 ppm for CH_2OH group were used to follow the progress of the reaction and growth of the dendrimers. The mass spectrometric analysis for dendrimers and dendrons exhibited the calculated molecular ion peak as an intense peak in most of the compounds. For dendrons and dendrimers with molecular weight less than 1000 Da, high-resolution ES-MS analysis could be performed successfully with the error less than 5 ppm between the observed and calculated mass position. Higher generation dendrimers **16–18** could not be analyzed by mass spectrometry. Also, reliable elemental analysis could not be obtained for the dendrons and dendrimers, due to the hygroscopic nature of these compounds.

2.5. Evaluation of the cytotoxic properties of dendrimers

PETIM dendrimers synthesized herein are similar in chemical constitution to polyether and polyamine polymers, which are studied extensively in biological studies.[4] Dendrimers with carboxylic acid groups at the peripheries were studied for hemolytic cleavage of red blood cells.[7] In vitro cytotoxic studies were carried out by MTT assay[8] on water soluble dendrimers incubated on two different cell lines human breast cancer T47D and African green monkey kidney CV-1. Cells were seeded at the density of 10,000 cells per well in a 96 well microtitre plate using bovine serum-containing medium. Cells were left to recover for 24 h, before the addition of fresh medium containing dendrimers and then incubated for 24 h. MTT was added and the cells were left for 2 h. The formazan formed was dissolved in optical grade DMF (20% w/v SDS in 50% DMF) and plates were read using a scanning multi-well spectrophotometer set at 570 nm. The viability of the cells exposed to dendrimers was expressed as percentage of the viability of cells with respect to control cell culture grown in the absence of dendrimers. Figure 1 shows the relative CV-1 cell viability of dendrimers **8**, **10**, **14** and **18** at different concentrations. The cell survival rate was more than 98% up to 100 mg/mL of the dendrimer solutions in both the cell lines T47D as well as CV-1. The MTT assay reveals that no measurable cytotoxicity is observed for these water-soluble dendrimers on both the cell lines.

3. Conclusion

We have developed a new method for the rapid synthesis of dendrons and dendrimers with a nitrogen as the core. The propyl ether–imine and carboxylic acid surface group functionalities of the dendrimers reported herein impart water solubility. In vitro cytotoxicity studies reveal that these new PETIM dendrimers are non-toxic. In the context of their facile synthesis and non-toxic properties, PETIM dendrimers have potential for a range of applications such as drug delivery, scaffolds for biomimetic chemistry and other biological studies, apart from their utility in chemical and materials related studies.

4. Experimental

4.1. General remarks

Chemicals *tert*-butyl acrylate, LAH and Ra-Co (Raney® 2700 cobalt) were purchased and were used as received. Acrylonitrile was purified by passing through neutral alumina before use. Solvents were dried and distilled according to the literature procedures. Analytical TLC was performed on commercial plates coated with aluminium oxide 60 F_{254} neutral (type E, 0.2 mm) or silica gel GF_{254} (0.25 mm). Silica gel (100–200 mesh) and basic alumina were used for column chromatography. Infrared spectra were recorded either neat or as KBr samples. Matrix-assisted laser desorption ionization-time-of-flight mass spectra (MALDI-TOF-MS) was performed using gentisic acid matrix. Electrospray and high-resolution mass spectra were performed on a Q-TOF mass spectrometer. ^1H and ^{13}C NMR spectral analysis were performed either on a spectrometer operating at 300 and 75 MHz, respectively, or on a 400 spectrometer operating at 400 and 100 MHz, respectively, with residual solvent signal acting as the internal standard. The following abbreviations are used to explain the multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet; band, several overlapping signals; b, broad.

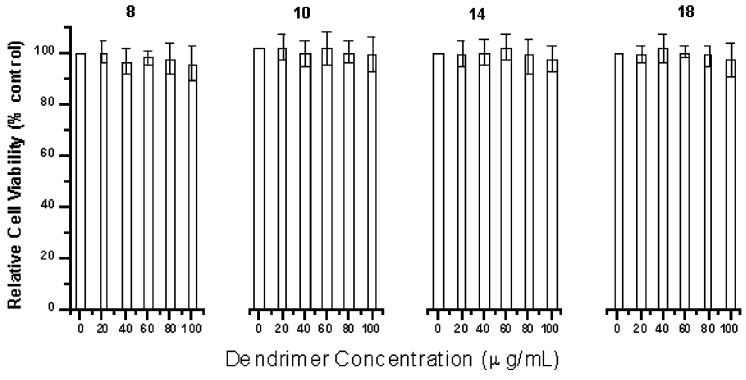


Figure 1. In vitro cytotoxicity studies of compounds **8**, **10**, **14** and **18** on African green monkey kidney CV-1 cell line, in the presence of dendrimers, at various concentrations.

4.2. General procedure for Michael addition of acrylonitrile (I)

Acrylonitrile was added to a mixture of alcohol and aqueous NaOH (40%) while maintaining the temperature below 30 °C. The reaction mixture was stirred for 6 h at room temperature, neutralized with aq HCl (1 M) and diluted with $CHCl_3$. The organic layer was washed with aqueous NaOH (5%) followed by brine, evaporated in vacuo and dried thoroughly to afford the desired Michael addition product.

4.3. General procedure for the reduction of nitrile using Ra-Co catalyst and subsequent Michael addition of resulting amine (II)

The nitrile derivative in MeOH was transferred to a hydrogenation reactor vessel and was admixed with Ra-Co catalyst in H_2O (40 mL). The mixture was hydrogenated (H_2, 40 atm) at 70 °C for 1 h, cooled, decanted and the solvents were evaporated to afford the amine as a colorless oil. A solution of the crude amine in MeOH (5 mL) was treated with *tert*-butyl acrylate and stirred for 6 h. Excess *tert*-butyl acrylate, solvents were removed in vacuo and the resulting product was purified (alumina).

4.4. General procedure for the reduction of *tert*-butyl esters (III)

To a suspension of LAH in THF at 0 °C, the ester in THF was added drop-wise for ~30 min. The suspension was stirred at 0 °C for 30 min., brought to room temperature and continued the stirring for additional 1 h. The reaction mixture was cooled to 0 °C, quenched with ice (~1 g), Na_2SO_4 (solid) was added and left aside till the grey residue became a free white suspension and settled. The suspension was passed through a plug of celite, the filtrate was dried and concentrated to obtain the alcohol as colorless liquid.

4.5. General procedure for the hydrolysis of *tert*-butyl esters (IV)

To a solution of the ester in CH_2Cl_2, AcCl and H_2O were added slowly. The solution was stirred at room temperature for 8 h. Solvents were removed in vacuo, the resulting residue triturated several times with hexane and CH_2Cl_2 to afford the desired acid as a white foamy solid.

4.5.1. Compound 1. A mixture of 3-aminopropan-1-ol (4.91 g, 65.4 mmol) and *tert*-butyl acrylate (21.87 g, 171.0 mmol) in MeOH (25 mL) were stirred at room temperature for 6 h. Excess of *tert*-butyl acrylate and solvent were removed in vacuo. The crude product was diluted with $CHCl_3$ and washed with brine. The organic layer was dried and concentrated to obtain **1** as colorless viscous liquid (21.3 g, 98%). FT-IR (neat) ν: 3429, 1729, 1459, 1368, 1158. ES-MS *m/z*: 332 $[M]^+$ (100%); 276 $[M+1-CMe_3]^+$ (53%). ^{1}H NMR ($CDCl_3$) δ: 1.42 (s, 18H), 1.66 (q, 2H, J=6.0 Hz), 2.37 (t, 4H, J=7.2 Hz), 2.60 (t, 2H, J=6.0 Hz), 2.72 (t, 4H, J=7.2 Hz), 3.71 (t, 2H, J=6.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 28.1, 28.4, 33.3, 49.4, 50.4, 63.2, 80.7, 171.7. HRMS *m/z*: calcd for $C_{17}H_{33}O_5N$: 332.2437. Found: 332.2440.

4.5.2. Compound 2. A solution of **1** (21.0 g, 63.4 mmol) in THF (25 mL) was added drop-wise to a suspension of LAH (7.22 g, 0.19 mol) in THF (150 mL), left stirring for 1 h and worked up as described in the general procedure III to obtain **2** a colorless liquid (12.0 g, 99%). Alternatively, a solution of **7** (21.0 g, 52.2 mmol) in THF (25 mL) was added drop-wise to a suspension of LAH (7.22 g, 0.19 mol) in THF (150 mL), left stirring for 1 h and worked up as described in the general procedure III to obtain **2** as a colorless liquid (10.0 g, 99%). FT-IR (neat) ν: 3349, 1466, 1375, 1058. CI-MS *m/z*: 192 $[M]^+$ (100%); 146 $[M-1-CH_2CH_2OH]^+$ (40%). ^{1}H NMR ($CDCl_3$) δ: 1.74 (q, 6H, J=6.3 Hz), 2.60 (t, 6H, J=6.3 Hz), 3.72 (t, 6H, J=6.3 Hz). ^{13}C NMR ($CDCl_3$) δ: 28.7, 52.1, 61.8. HRMS *m/z*: calcd for $C_9H_{21}O_3N$: 192.1599. Found: 192.1602.

4.5.3. Compound 3. Acrylonitrile (3.36 g, 63.4 mmol) was added to a mixture of **2** (6.0 g, 31.3 mmol) and aq NaOH (40%) (0.31 mL), stirred for 6 h and worked up as given in the general procedure I to afford **3** as a colorless liquid (3.58 g, 38%). FT-IR (neat) ν: 3452, 2251, 1466, 1222, 1112, 1060. CI-MS *m/z*: 298 $[M]^+$ (100%). ^{1}H NMR ($CDCl_3$) δ: 1.69–1.79 (m, 6H), 2.52–2.64 (m, 10H), 3.52 (t, 4H, J=6.3 Hz), 3.63 (t, 4H, J=6.3 Hz), 3.76 (t, 2H, J=6.3 Hz). ^{13}C NMR ($CDCl_3$) δ: 18.9, 26.9, 27.8, 50.7, 55.1, 64.5, 65.3, 69.2, 117.9. HRMS *m/z*: calcd for $C_{15}H_{27}O_3N_3$: 298.2130. Found: 298.2131.

4.5.4. Compound 4. Colorless liquid (1.53 g, 20%). FT-IR (neat) ν: 3394, 2251, 1466, 1222, 1116, 1060. EI-MS *m/z*: 243 $[M-1]^+$ (2%); 199 $[M-CH_2CH_2OH]^+$ (24%); 155 $[M-1-2\times CH_2CH_2OH]^+$ (39%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.69–1.79 (m, 6H), 2.52–2.64 (m, 8H), 3.52 (t, 2H, J=6.3 Hz), 3.63 (t, 2H, J=6.3 Hz), 3.73 (t, 4H, J=6.3 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 18.9, 26.9, 28.5, 50.7, 52.8, 62.6, 65.3, 69.2, 117.9.

4.5.5. Compound 5. Colorless liquid (2.19 g, 20%). Alternatively, **5** was synthesized upon reaction of **2** (12.0 g, 62.6 mmol) with acrylonitrile (9.95 g, 0.18 mol) and aq NaOH (40%) (0.62 mL) for 6 h. After work up as given in the general procedure I, **5** was isolated, as a colorless liquid (21.2 g, 96%). FT-IR (neat) ν: 2251, 1470, 1368, 1116. ES-MS *m/z*: 351 $[M]^+$ (100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.78 (q, 6H, J=6.3 Hz), 2.58–2.64 (m, 12H), 3.54 (t, 6H, J=6.3 Hz), 3.64 (t, 6H, J=6.3 Hz). ^{13}C NMR (75.5 MHz. $CDCl_3$) δ: 18.9, 26.7, 50.6, 65.3, 69.1, 118.0. HRMS: calcd for $C_{18}H_{30}O_3N_4$: *m/z*: 351.2396 $[M]^+$. Found: 351.2395 $[M]^+$.

4.5.6. Compound 6. The bis-nitrile **3** (0.50 g, 1.67 mmol) in MeOH (0.5 mL) was added with Ra-Co catalyst in H_2O (40 mL). The reaction was stirred for 1 h and the reaction mixture was worked up as given in the general procedure II to afford the amine intermediate. A solution of crude amine (0.50 g, 1.65 mmol) in MeOH (5 mL) was treated with *tert*-butyl acrylate (4.37 g, 34.1 mmol), and the reaction was followed as given in general procedure II, to afford, after purification (alumina) (hexane/EtOAc, 85:15) **6**, as a colorless liquid (1.28 g, 94% combined yield for nitrile reduction and Michael addition). FT-IR (neat) ν: 3440, 1729, 1461, 1367, 1157. ES-MS *m/z*: 819 $[M]^+$ (100%). ^{1}H NMR ($CDCl_3$) δ: 1.43 (s, 36H), 1.68 (b, 10H), 2.34 (t, 8H,

J=7.2 Hz), 2.47 (m, 8H), 2.64 (t, 2H, J=5.7 Hz), 2.68 (t, 8H, J=7.2 Hz), 3.38 (b, 8H), 3.77 (t, 2H, J=5.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 27.1, 27.6, 28.1, 29.7, 33.8, 49.4, 50.5, 51.0, 54.9, 64.4, 69.0, 80.2, 172.1. HRMS *m/z*: calcd for $C_{43}H_{83}O_{11}N_3$: 818.6106. Found: 818.6103.

4.5.7. Compound 7. Ammonia (0.90 g, 53 mmol) and *tert*-butyl acrylate (21.87 g, 171.0 mmol) in MeOH (25 mL) were stirred at room temperature for 6 h. Excess of *tert*-butyl acrylate and solvent were removed in vacuo, dried and concentrated to obtain **7**, as colorless viscous liquid (21.0 g, 98%). FT-IR (neat) ν: 1730, 1456, 1368, 1154. EI-MS *m/z*: 402 $[M]^+$ (100%); 424 $[M+Na]^+$ (55%); 440 $[M+K]^+$ (45%). ^{1}H NMR ($CDCl_3$): δ: 1.42 (s, 27H), 2.34 (t, 6H, J= 7.2 Hz), 2.71 (t, 6H, J=7.2 Hz). ^{13}C NMR ($CDCl_3$) δ: 28.1, 33.9, 49.2, 80.2, 171.9. HRMS *m/z*: calcd for $C_{21}H_{39}O_6N$: 402.2855. Found: 402.2842.

4.5.8. Compound 8. To a solution of **7** (0.85 g, 2.1 mmol) in CH_2Cl_2 (25 mL), AcCl (4.6 mL) and H_2O (1.08 mL) were added. The deprotection reaction was continued and worked up as given in the general procedure IV for the hydrolysis of *tert*-butyl esters to afford **8** as a white foamy solid (0.49 g, 99%). FT-IR (KBr) ν: 3096, 1754, 1716, 1402, 1180. ES-MS *m/z*: 234 $[M+1]^+$ (100%); 256 $[M+Na]^+$ (20%); 174 $[M-CH_2CO_2H]^+$ (36%). ^{1}H NMR (D_2O) δ: 2.85 (t, 6H, J=6.0 Hz), 3.37 (t, 6H, J=6.0 Hz). ^{13}C NMR (D_2O) δ: 28.1, 50.0, 174.5.

4.5.9. Compound 9. Tris-nitrile **5** (0.80 g, 2.2 mmol) in MeOH (0.5 mL) was added with Ra-Co catalyst in H_2O (40 mL). The reaction was stirred for 1 h and the reaction mixture was worked up as given in the general procedure II to afford the amine intermediate. A solution of crude amine (0.82 g, 2.2 mmol) in MeOH (5 mL) was treated with *tert*-butyl acrylate (4.37 g, 34.1 mmol), and the reaction was followed as given in general procedure II, to afford, after purification (alumina) (hexane/EtOAc, 95:5) **9**, as a colorless liquid (2.33 g, 90% combined yield for nitrile reduction and Michael addition). FT-IR (neat) ν: 1729, 1457, 1367, 1158. ES-MS *m/z*: 1132 $[M]^+$ (75%); 872 $[M-2(CH_2CH_2CO_2\,{}^tBu)]^+$ (46%). ^{1}H NMR ($CDCl_3$): δ: 1.41 (s, 54H), 1.66 (m, 12H), 2.32 (t, 12H, J=7.2 Hz), 2.44 (t, 12H, J= 7.2 Hz), 2.68 (t, 12H, J=7.2 Hz), 3.37 (m, 12H). ^{13}C NMR ($CDCl_3$) δ: 28.1, 33.7, 49.4, 50.5, 68.9, 80.2, 172.1.

4.5.10. Compound 10. To a solution of **9** (0.85 g, 2.1 mmol) in CH_2Cl_2 (25 mL), AcCl (4.6 mL) and H_2O (1.08 mL) were added. The deprotection reaction was continued and worked up as given in the general procedure IV for the hydrolysis of *tert*-butyl esters to afford **10**, as a white foamy precipitate (0.49 g, 99%). FT-IR (neat) ν: 2568, 1729, 1416, 1186. ES-MS *m/z*: 796 $[M+1]^+$ (100%); 723 $[M-CH_2CH_2CO_2H]^+$ (51%); 651 $[M+1-2\times CH_2CH_2CO_2H]^+$ (34%). ^{1}H NMR (D_2O) δ: 1.85 (b, 12H), 2.80 (t, 12H, J=6.4 Hz), 3.14 (b-t, 6H), 3.21 (t, 6H, J=6.4 Hz), 3.37 (t, 12H, J=6.4 Hz), 3.46 (t, 6H, J=6.0 Hz), 3.50 (t, 6H, J= 6.0 Hz). ^{13}C NMR (100 MHz, D_2O) δ: 24.0, 24.2, 29.2, 50.3, 51.4, 53.0, 68.4, 68.8, 175.1.

4.5.11. Compound 11. A solution of **9** (3.78 g, 3.3 mmol) in THF (15 mL) was added dropwise to a suspension of LAH (0.90 g, 23.7 mmol) in THF (100 mL), left stirring for 1 h and worked up as described in the general procedure III to obtain **11**, as a colorless liquid (2.27 g, 99%). FT-IR (neat) ν: 3378, 1465, 1375, 1113, 1061. ES-MS *m/z*: 712 $[M+1]^+$ (56%); 356 $[M+1/2]^+$ (100%). ^{1}H NMR ($CDCl_3$) δ: 1.74 (m, 24H), 2.46 (m, 18H), 2.57 (t, 6H, J=6.3 Hz), 3.37–3.42 (m, 12H), 3.68 (t, 12H, J=5.7 Hz). ^{13}C NMR ($CDCl_3$) δ: 26.8, 27.1, 28.6, 50.7, 50.9, 52.8, 62.7, 68.7, 69.1. HRMS *m/z*: calcd for $C_{36}H_{78}O_9N_4$: 711.5847. Found: 711.5855.

4.5.12. Compound 12. Acrylonitrile (0.89 g, 16.8 mmol) was added to a mixture of **11** (1.66 g, 2.34 mmol) and aq NaOH (40%, 0.15 mL), stirred for 6 h and worked up as given in the general procedure I to obtain crude product which was purified on alumina ($CHCl_3$/MeOH, 98:2) to afford compound **12**, as a colorless liquid (2.35 g, 97%). FT-IR (neat) ν: 2251, 1652, 1368, 1118. ES-MS *m/z*: 1030 $[M+1]^+$ (100%); 750 $[M-C_{15}H_{26}N_3O_2]^+$ (55%); 515 $[M+1/2]^+$ (62%). ^{1}H NMR ($CDCl_3$) δ: 1.65–1.75 (m, 24H), 2.43–2.50 (m, 24H), 2.60 (t, 12H, J=6.3 Hz), 3.40 (t, 12H, J=6.3 Hz), 3.52 (t, 12H, J=6.3 Hz), 3.63 (t, 12H, J=6.3 Hz). ^{13}C NMR ($CDCl_3$) δ: 18.8, 27.3, 27.4, 50.4, 50.7, 65.2, 69.0, 69.4, 117.9. HRMS *m/z*: calcd for $C_{54}H_{96}O_9N_{10}$: 1029.7440. Found: 1029.7428.

4.5.13. Compound 13. Hexa-nitrile **12** (0.35 g, 0.34 mmol) in MeOH (0.5 mL) was added with Ra-Co catalyst in H_2O (40 mL). The reaction was stirred for 1 h and the reaction mixture was worked up as given in the general procedure II to afford the amine intermediate. A solution of crude amine (0.36 g, 0.34 mmol) in MeOH (5 mL) was treated with *tert*-butyl acrylate (4.37 g, 34.1 mmol), and the reaction was followed as given in general procedure II, to afford, after purification (alumina) (hexane/EtOAc, 60:40) **13**, as a colorless liquid 0.88 g (70% combined yield for nitrile reduction and Michael addition). FT-IR (neat) ν: 1729, 1461, 1367, 1255, 1157. ES-MS *m/z*: 2591 $[M+1]^+$ (14%). ^{1}H NMR ($CDCl_3$) δ: 1.44 (s, 108H), 1.68 (q, 36H, J= 6.6 Hz), 2.34 (t, 24H, J=6.9 Hz), 2.46 (b-t, 36H, J= 6.6 Hz), 2.71 (t, 24H, J=6.9 Hz), 3.39 (app t, 36H). ^{13}C NMR ($CDCl_3$) δ: 27.4, 27.7, 28.1, 33.8, 49.4, 50.6, 50.9, 68.9, 69.3, 80.2, 172.0.

4.5.14. Compound 14. To a solution of **13** (0.70 g, 0.27 mmol) in CH_2Cl_2 (25 mL), AcCl (1.4 mL) and H_2O (0.32 mL) were added. The deprotection reaction was continued and worked up as given in the general procedure IV for the hydrolysis of *tert*-butyl esters to afford **14**, as a foamy precipitate (0.51 g, 99%). FT-IR (neat) ν: 2568, 1729, 1416, 1186. MALDI-TOF-MS *m/z*: 1946 $[M+2+Na]^+$ (65%). ^{1}H NMR (D_2O) δ: 1.83 (b, 36H), 2.78 (t, 24H, J=6.3 Hz), 3.14 (b, 36H), 3.33 (t, 24H, J=6.3 Hz), 3.37 (b-t, 36H). ^{13}C NMR (D_2O) δ: 24.0, 24.2, 29.1, 50.3, 51.9, 53.1, 68.3, 68.8, 174.8.

4.5.15. Compound 15. A solution of **13** (0.27 g, 0.1 mmol) in THF (5 mL) was added drop wise to a suspension of LAH (0.06 g, 1.4 mmol) in THF (100 mL) left stirring for 1 h and worked up as described in the general procedure III to obtain **15** a colorless liquid (0.12 g, 66%). FT-IR (neat) ν: 3372, 1464, 1365, 1113, 1062. ES-MS *m/z*: 1750 $[M]^+$. ^{1}H NMR ($CDCl_3$) δ: 1.67–1.75 (m, 60H), 2.50–2.63 (m, 36H), 2.61 (t, 24H, J=6.3 Hz), 3.46–3.48 (m, 36H), 3.69–3.75 (m, 24H).

^{13}C NMR ($CDCl_3$) δ: 26.7, 28.5, 28.7, 29.8, 50.8, 52.0, 52.7, 61.0, 61.6, 62.3, 68.7.

4.5.16. Compound 16. Acrylonitrile (0.07 g, 1.4 mmol) was added to a mixture of **15** (0.18 g, 0.1 mmol) and aq NaOH (40%, 14 μL), stirred for 6 h and worked up as given in the general procedure I to obtain crude product which was purified (alumina) ($CHCl_3$/MeOH, 98:2) to afford compound **16**, as a colorless liquid (0.19 g, 77%). FT-IR (neat) ν: 2251, 1652, 1368, 1118. ^{1}H NMR ($CDCl_3$) δ: 1.67–1.76 (m, 60H), 2.45–2.52 (m, 60H), 2.60 (t, 24H, J=6.3 Hz), 3.41 (m, 12H, J=6.3 Hz), 3.52 (t, 24H, J=6.3 Hz), 3.64 (t, 24H, J=6.3 Hz), 3.72 (t, 24H, J=6.3 Hz). ^{13}C NMR ($CDCl_3$) δ: 18.8, 27.3, 27.4, 50.5, 50.8, 65.9, 69.0, 69.4, 117.4.

4.5.17. Compound 17. The nitrile **16** (0.09 g, 0.037 mmol) in MeOH (0.5 mL) was added with Ra-Co catalyst in H_2O (40 mL). The reaction was stirred for 1 h and the reaction mixture was worked up as given in the general procedure II to afford the amine intermediate. A solution of crude amine (0.09 g, 0.034 mmol) in MeOH (5 mL) was treated with *tert*-butyl acrylate (4.37 g, 34.1 mmol) and the reaction was followed as given in general procedure II, to afford, after purification (alumina) (hexane/EtOAc, 40:60) **17**, as a colorless liquid 0.04 g (18% combined yield for nitrile reduction and Michael addition). FT-IR (neat) ν: 1729, 1458, 1367, 1254, 1158. ^{1}H NMR ($CDCl_3$) δ: 1.44 (s, 216H), 1.68 (m, 84H), 2.34 (t, 48H, J=7.2 Hz), 2.46 (app t, 84H), 2.71 (t, 48H, J=7.2 Hz), 3.39 (m, 84H). ^{13}C NMR ($CDCl_3$) 27.6, 28.1, 29.7, 33.8, 49.4, 50.5, 50.8, 68.9, 80.2, 172.0.

4.5.18. Compound 18. To a solution of **17** (0.028 g, 0.5 μmol) in CH_2Cl_2 (25 mL), AcCl (52 μL) and H_2O (12 μL) were added. The deprotection reaction was continued and worked up as given in the general procedure IV to afford **18**, as a foamy precipitate (0.021 g, 99%). FT-IR (neat) ν: 2568, 1729, 1416, 1186. ^{1}H NMR (D_2O) δ: 1.83 (b, 84H), 2.78 (t, 48H, J=6.3 Hz), 3.14 (b, 84H), 3.33 (t, 48H, J=6.3 Hz), 3.37 (b-t, 84H). ^{13}C NMR (D_2O) δ: 24.0, 24.2, 29.1, 29.8, 49.8, 51.3, 51.4, 52.2, 53.6, 68.4, 68.5, 174.8.

4.6. Cytotoxicity studies (MTT assay)

African green monkey kidney CV-1 or human breast cancer T47D cells were seeded at a density of 10,000 cells/well in 96-well plate and grown in 95 μL of culture medium supplemented with 10% fetal bovine serum for 24 h. Following exposure of the cells with 5 μL of aqueous solutions of dendrons or dendrimers for 24 h, 25 μL of 5 mg/mL stock solution of 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) were added to each well. After 2 h of incubation at 37 °C, 100 μL of extraction buffer (containing 20% w/v SDS in a solution of 50% of DMF, pH 4.7) was added. Absorbance was measured at 570 nm after an overnight incubation at 37 °C.

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A convenient palladium catalyzed synthesis of symmetric biaryls, biheterocycles and biaryl chiral diamides

Shyamaprosad Goswami,[a,*] Avijit Kumar Adak,[a] Reshmi Mukherjee,[a,†] Subrata Jana,[a] Swapan Dey[a] and John F. Gallagher[b,‡]

[a]*Department of Chemistry, Bengal Engineering and Science University, Shibpur, Howrah 711103, West Bengal, India*
[b]*School of Chemical Sciences, Dublin City University, Dublin 9, Ireland*

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Abstract—A series of symmetrical diamido biaryls has been synthesized in good yield by direct homocoupling of iodoarylbenzamides by palladium-catalysis. No cross product has been isolated from the reaction mixture of two different iodoarylbenzamides under similar conditions. However, only in the case of 2-iodo-*N*-phenylbenzamide, the intramolecularly coupled product phenanthridone has been isolated as a minor product along with the major intermolecularly coupled product. Biphenyl chiral diamides have been synthesized by this coupling method. This coupling reaction also works well with the reductive dimerization of functionalized heterocyclic compounds. Thus 6,6′-dipivaloylamino-3,3′-bipyridine and 6,6′-dimethyl-2,2′-bipyridine have been efficiently synthesized. In two cases, the X-ray crystal structures have been solved to establish the structures of symmetrical and chiral diamido biaryls and their supramolecular networks.

1. Introduction

Highly functionalized symmetrical biaryl subunits are present in a large number of natural products such as tellimagrandins,[1a] (−) gossypol[1b] and are also used in materials science as precursors to rigid liquid crystals[1c] as well as semi conducting complexes, and consequently gain much attention for their synthesis.[1e] There are various coupling methods, and the application of these methods have been recently reviewed.[2] The most convenient method for the synthesis of symmetrical biaryls is reductive homocoupling of arylhalides either by Ullmann synthesis[3] or by oxidative coupling of arylboronic acid,[4a] arylzinc,[4b] arylstannanes[4c] and aryl mesylates.[4d] However, palladium catalyzed coupling reactions are among the most important C–C bond forming reactions in organic synthesis.[5] Lemaire et al.[6] have synthesized functionalized symmetrical biaryls and biheterocycles via the homocoupling of aryl halides using $Pd(OAc)_2$ in the presence of *n*-Bu_4NBr and K_2CO_3. However, palladium catalyzed reductive homocoupling of aryl halides using ionic liquid[7] and zinc powder-formate salt[8] are also known.

Keywords: Symmetric biaryls; Palladium catalyzed reaction; Homocoupling; Ullmann reaction; Biaryl chiral diamides.
* Corresponding author. Tel.: +91 3326684561; fax: +91 3326682916; e-mail: spgoswamical@yahoo.com
† Presently at the University of Zurich, Switzerland.
‡ Fax: +353 1 7005503.

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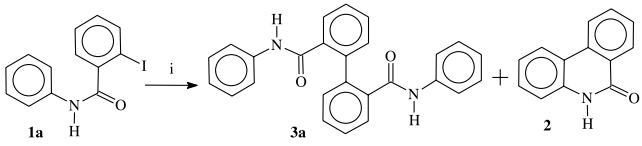
2. Results and discussion

We report here the results of our observation of palladium catalyzed reaction of iodoarylbenzamides to prepare symmetrical biaryl diamides, including biaryl chiral diamides, by a modified procedure. During our investigation of the palladium catalyzed homocoupling reaction of **1a** by using $(Ph_3P)_2PdCl_2$ as a catalyst, we have unexpectedly isolated an intramolecularly coupled product **2** (15–20%) as a minor product (Scheme 1).

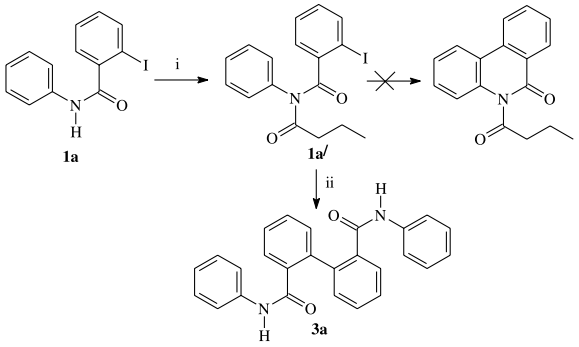


Scheme 1. (i) $(Ph_3P)_2PdCl_2$, CuI, Et_3N, DMF, 120 °C, 12 h.

The symmetrical diamido biaryls **3a–g** was synthesized in good yields from direct self-coupling of iodoarylbenzamides **1a–g** along with the biaryl chiral diamides **5** and **6** by palladium catalyzed reactions. No cross product was isolated from the reaction mixture of **1a** and **1b** under similar conditions. Only in the case of **1a**, did cyclization leading to a phenanthridone **2** occur. The crystal structures of **3a** (N^2,$N^{2\prime}$-diphenyl [1,1′-biphenyl]-2,2′-dicarboxamide) and **6** (biphenyl-2,2′-dicarboxylic acid bis-[(1*R*-phenylethyl)-amide]) reveal the detailed structures of symmetrical

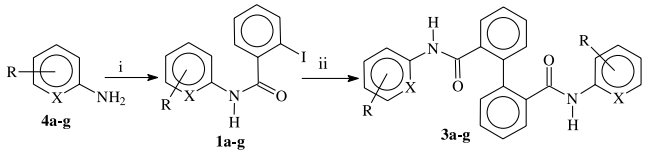
and chiral diamido biaryls and their interesting supramolecular networks.

According to the reported procedure,[9a] it is necessary to protect the N–H function of **1a** with an alkyl group to obtain the cyclized product **2** (*N*-protected) by a palladium catalyzed dehydrohalogenation reaction since palladium forms a cyclic complex between the halogen bearing carbon and the N–H function. However, the *N*-butyryl protected derivative of 2-iodo-*N*-phenyl-benzamide **1a** formed the intermolecularly coupled product **3a** in the Heck reaction[9b] using tri-*o*-tolylphosphine, palladium acetate and sodium carbonate in DMF under reflux for one and a half hours where selective deprotection of the *N*-butyryl group occurred (Scheme 2).



Scheme 2. (i) Butyryl chloride, Et_3N, dry C_6H_6, reflux, 24 h; (ii) $Pd(OAc)_2$, $(o\text{-tol})_3P$, Na_2CO_3, DMF, reflux, 1.5 h.

Intramolecular palladium catalyzed reactions are well established in the synthesis of benzo[*c*]phenanthridine or fully aromatized phenanthridine alkaloids.[9b–e] Interestingly when **1a** was subjected to $Pd(PPh_3)_2Cl_2$ catalyzed coupling reaction, the major product was the intermolecularly coupled diphenyl diamide **3a** along with the minor intramolecularly coupled product phenanthridinone **2**. Then **1a** was subjected to a reaction using $Pd(OAc)_2$ as the catalyst with Ph_3P and Et_3N, and no intramolecularly coupled product **2** was obtained but the only isolated product was the biaryl, **3a**. This homocoupling reaction was then performed with a series of 2-iodo-*N*-arylbenzamides **1a–e** using a variety of catalysts and solvents, for example, $Pd(Ph_3P)_2Cl_2$/CuI, $Pd(OAc)_2/Ph_3P$/CuI, $Pd(OAc)_2/(o\text{-tolyl})_3P$/CuI in DMF or acetonitrile and with a base, Et_3N. However, the best conditions were to use a catalytic amount of $Pd(OAc)_2/Ph_3P$/CuI and Et_3N in refluxing acetonitrile. This catalyst system was also examined with heterocyclic compounds, for example, 2-iodo-*N*-pyridin-2-ylbenzamides **1f–g**. In all these cases, 2-iodo-*N*-arylbenzamides **1a–g** (obtained from the corresponding amines **4a–g**) underwent conversion only to biaryls **3a–g** in good yields showing the generality of this method for the intermolecular biaryl coupling reactions (Scheme 3).



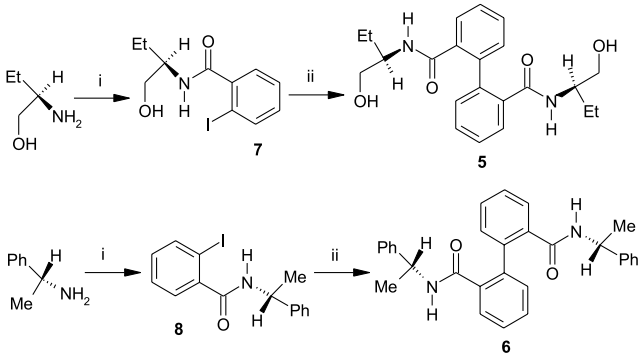
Scheme 3. (i) 2-Iodobenzoyl chloride (1.1 equiv), dry CH_2Cl_2, Et_3N, rt; (ii) $Pd(OAc)_2$, PPh_3, CuI, Et_3N, acetonitrile, reflux, 6–8 h.

Table 1. Yield of products (**3a–g**) of palladium catalyzed coupling reactions of **1a–g**

Entry	2-Iodo-*N*-arylbenzamides (**1a–g**)	Symmetrical diamido-biaryls (**3a–g**)	Yield (%)
1.	**1a**: X=CH, R=H	**3a**: X=CH, R=H	70
2.	**1b**: X=CH, R=2-Me	**3b**: X=CH, R=2-Me	66
3.	**1c**: X=CH, R=3-Me	**3c**: X=CH, R=3-Me	70
4.	**1d**: X=CH, R=4-OMe	**3d**: X=CH, R=4-OMe	68
5.	**1e**: X=CH, R=4-CO_2Et	**3e**: X=CH, R=4-CO_2Et	56
6.	**1f**: X=N, R=H	**3f**: X=N, R=H	54
7.	**1g**: X=N, R=6-Me	**3g**: X=N, R=6-Me	65

The results of the palladium catalyzed homocoupling reactions of various iodoarylbenzamides are shown in Table 1.

We have prepared the biphenyl chiral diamides **5** and **6** from **7** and **8**, respectively, (Scheme 4). Protection of the hydroxyl group in *R*(−)-2-amino-1-butanol was not necessary as evident by the following observation. Reaction of *R*(−)-2-amino-1-butanol with 2-iodobenzoyl chloride afforded the chiral 2-iodobenzamide **7**. Subsequent coupling of **7** gave the biphenyl chiral diamide **5** as a brown-semi solid in 54% yield using similar conditions as before.



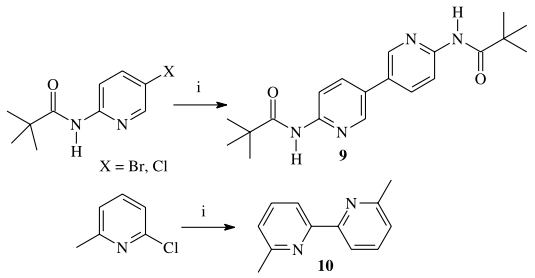
Scheme 4. (i) 2-Iodobenzoyl chloride, dry CH_2Cl_2, Et_3N, rt, 6 h; (ii) $Pd(OAc)_2$, Ph_3P, CuI, Et_3N, CH_3CN, reflux, 6–8 h.

Similarly, *R*(+)-α-methylbenzylamine was converted to the iodobenzamide **8** which on palladium catalyzed coupling reaction afforded the biphenyl chiral diamide **6** as a white crystalline solid in 70% yield.

The coupling reaction using these conditions was also found to be successful with the synthesis of homocoupled bi-heterocyclic compounds. These compounds are useful for molecular recognition research and in metal directed assembly and also in the synthesis of metal helicates.[10]

Thus 3,3′- and 2,2′- coupled functionalized bipyridyl compounds **9** and **10** were synthesized efficiently by this method (Scheme 5). For the 3,3′-coupling reaction, 2-*N*-pivaloyl-3-bromopyridine required 12 h at reflux in comparison to the chloro analog, which required 46 h.

All of the biaryls were characterized by ^1H NMR and also by mass spectrometric studies. Single crystal X-ray diffraction[11] studies in two cases (achiral **3a** and chiral **6**) confirmed their biphenyl structures.



Scheme 5. (i) $Pd(OAc)_2$, Ph_3P, CuI, Et_3N, CH_3CN, reflux, 12–40 h.

As depicted in Figure 1, the biaryl **3a** is biphenyl-2,2′-dicarboxylic acid 2′-amide 2-phenylamide. Interestingly, the supramolecular structure of the biphenyl diamide shows that one amide oxygen accepts two intermolecular hydrogen bonds {N–H and C–H from another molecule, graph set $C(4)$, $R_2^1(6)$, N···O 2.857(6) Å and C···O 3.313(8) Å with N–H···O/C–H···O 165 and 137°, respectively} together with the *trans* amide NH which forms one intramolecular hydrogen bond with amide oxygen, set $S(9)$, N···O 2.857(6) Å N···O 2.919(6) Å. These geometric values have similar dimensions to those found in related intermolecular hydrogen bonding amide···amide systems as *N*-H···O=C hydrogen bonds with graph-set C(4).[12]

However, the intermolecular hydrogen bonding in **3a** displays a six-membered hydrogen bonding motif involving the adjacent amido NH and phenyl CH moieties interacting with the amide oxygen of a symmetry related molecule. This motif is absent in the chiral analogue **6** (Fig. 2), which only shows the normal N–H···O=C type hydrogen bonding, N···O 2.912(3) Å, N–H···O 163°. This is perhaps due to the extra rigidity of the geometry in **6** together with the presence of a chiral centre between the amide NH and the phenyl group.

In both the biphenyl diamides (achiral **3a** and chiral **6**), the biphenyl rings are shown close to be perpendicular by the presence of only one amide group at the α position to each ring. The central rings are at angles 78.9° for **3a** (in tetragonal system) and 78.38° (in orthorhombic system).

3. Conclusion

We thus present here an efficient method for the preparation

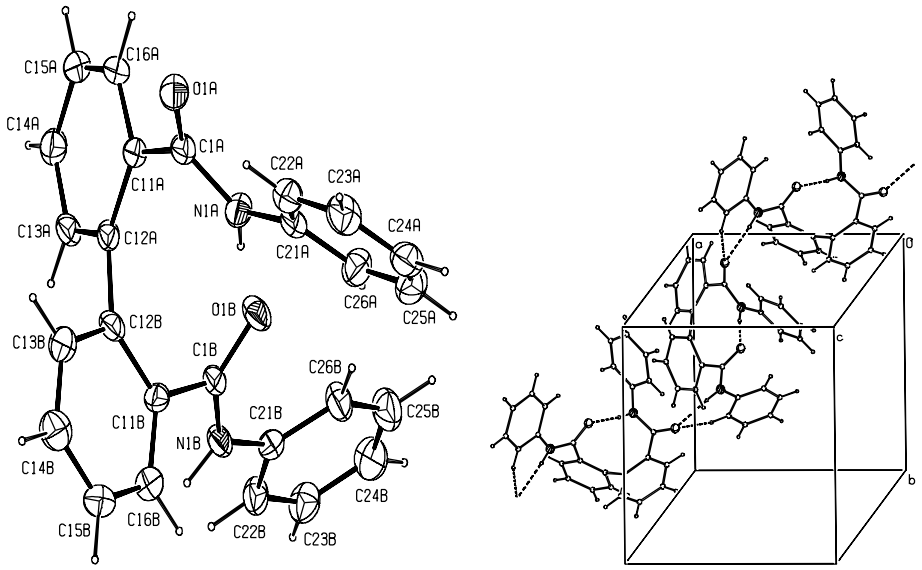


Figure 1. X-ray crystal structure of **3a** (above left) together with a view of the interactions (above right).

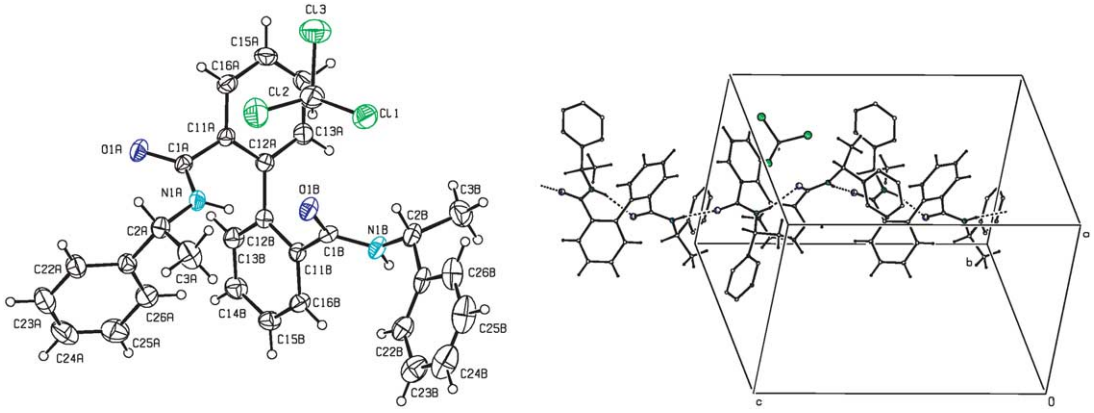


Figure 2. X-ray crystal structure of **6** (above left) together with a view of the interactions (above right).

of symmetrical diamido biaryls by palladium catalyzed homocoupling reaction as well as for the preparation of biphenyl chiral amides. The advantage is that we get the reductive coupling instead of dehalogenative coupling or simple reduction products, even though we have used palladium salt in the presence of Et_3N in an aprotic solvent like CH_3CN or DMF. The coupling reaction also works well in the synthesis of biheterocycles, for example, functionalized bipyridyls depending on the position of halogens. The crystal structures of achiral **3a** and chiral **6** were solved to confirm their structures along with exploring the amide–amide hydrogen bond induced supramolecular network in biphenyl 1,1′-diamides. We are currently investigating the application of this methodology in the synthesis of biphenyl or biheterocyclic designed molecules containing suitable amide substrates for studies in molecular recognition and supramolecular chemistry.

4. Experimental

All the reactions were carried out under nitrogen atmosphere in anhydrous solvents. CH_2Cl_2, DMF and Et_3N were distilled over CaH_2 and CH_3CN over P_2O_5. All chromatographic separations were performed on silica gel (100–200 mesh). For preparative thin layer chromatographic (PTLC) purification, the layer was formed on a glass plate using water gel-GF 254 silica gel. The petroleum ether used has a boiling range of 40–60 °C. Mps were uncorrected. ^{1}H NMR spectra were recorded either on a Bruker AM 300L MHz or a Bruker 500 MHz spectrometer. ^{13}C NMR spectra were recorded on a Bruker 500 MHz spectrometer. For NMR spectra, $CDCl_3$ was used as solvent unless otherwise mentioned using TMS as internal standard. Chemical shifts are expressed in δ unit and ^{1}H–^{1}H, ^{1}H–C coupling constants in Hz. IR spectra were recorded on a Perkin–Elmer Spectrum I spectrophotometer using KBr discs. Optical rotations are measured in a JASCO DIP 360 polarimeter. Mass spectra (JEOL JMS600) were obtained from the Indian Institute of Chemical Biology, Kolkata and the Philipps-Universitat, Marburg, Germany.

4.1. General procedure for the preparation of 2-iodo-*N*-arylbenzamides

To a magnetically stirred solution of the amines (1.0 mmol) in dry CH_2Cl_2 (20 ml) and freshly distilled Et_3N (1.2 equiv), was added 2-iodobenzoyl chloride (1.1 equiv), and stirring was continued for 6–12 h. The triethylamine hydrochloride was filtered off, and the organic layer after washing with water was dried (anhydrous Na_2SO_4) and then the solvent was removed under reduced pressure. The residue was purified using silica-gel chromatography to afford the corresponding 2-iodo-*N*-arylbenzamides (**1a**–**g**), **7** and **8** in almost quantitative yields.

Representative data for iodoarylbenzamides were as follows.

4.1.1. 2-Iodo-*N*-phenyl-benzamide (1a). Yield: (98%); off-white powder; mp 140–142 °C [lit.[13] 143–145 °C]. FT-IR (KBr): 3446, 2360, 1698, 1299, 696 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm)=7.97 (d, 1H, J=7.8 Hz), 7.70–7.39 (m, 6H), 7.25–7.17 (m, 2H), 6.60 (br. S, 1H, N*H*, D_2O exchangeable).

4.1.2. 2-Iodo-*N*-*o*-tolyl-benzamide (1b).[14] Yield: (96%); white crystalline solid; mp 195–197 °C. FT-IR (KBr): 3342, 1649, 1523, 1456, 1310, 1016, 753, 669 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm)=8.01 (d, 1H, J=7.9 Hz), 7.92 (d, 1H, J=7.8 Hz), 7.55 (d, 1H, J=7.2 Hz), 7.45 (t, 1H, J=7.3 Hz), 7.31–7.22 (m, 2H), 7.25 (br s, 1H, N*H*), 7.19–7.11 (m, 2H), 2.36 (s, 3H).

4.1.3. 2-Iodo-*N*-*m*-tolyl-benzamide (1c).[14] Yield: (95%); white solid; mp 155–157 °C. FT-IR (KBr): 3243, 1652, 1541, 1316, 779, 740 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm)=7.92 (d, 1H, J=7.9 Hz), 7.51 (s, 1H), 7.46–7.41 (m, 3H), 7.38 (br s, 1H, N*H*), 7.29–7.24 (m, 1H), 7.15 (t, 1H, J=7.6 Hz), 6.99 (d, 1H, J=7.4 Hz), 2.39 (s, 3H).

4.1.4. 2-Iodo-*N*-(4-methoxy-phenyl)-benzamide (1d).[14] Yield: (95%); white solid; mp 155–157 °C. FT-IR (KBr): 3308, 1651, 1513, 825, 741 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm)=7.90 (d, 1H, J=7.8 Hz), 7.57–7.50 (m, 3H), 7.42 (t, 1H, J=7.3 Hz), 7.37 (br s, 1H, N*H*), 7.14 (t, 1H, J=7.6 Hz), 6.92 (d, 2HH, J=8.9 Hz), 3.81 (s, 3H).

4.1.5. 4-(2-Iodo-benzoylamino)-benzoic acid ethyl ester (1e). Yield: (90%); cream colored solid; mp 110–112 °C. FT-IR (KBr): 3331, 1701, 1664, 1598, 1533, 1405, 1281, 1174, 1017, 769, 752, cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm)=8.07 (d, 1H, J=8.6 Hz), 7.93 (d, 1H, J=7.7 Hz), 7.85 (d, 1H, J=8.6 Hz), 7.72 (d, 1H, J=8.4 Hz), 7.65 (br s, 1H, N*H*), 7.54 (d, 1H, J=8.5 Hz), 7.45 (d, 1H, J=7.4 Hz), 7.17 (t, 1H, J=7.5 Hz), 6.64 (d, 1H, J=6.9 Hz), 4.37 (q, 2H, J=7.1 Hz), 1.40 (t, 3H, J=7.1 Hz). Anal. Calcd for $C_{16}H_{14}NO_3I$: C, 48.62; H, 3.57; N, 3.54. Found: C, 48.60; H, 3.60; N, 3.58.

4.1.6. 2-Iodo-*N*-pyridin-2-yl-benzamide (1f). Yield: (88%); cream colored solid; mp 92–94 °C. FT-IR (KBr): 2977, 1681, 1579, 1433, 1309, 1015, 780 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm)=10.15 (br s, 1H, N*H*), 8.52 (d, 1H, J=8.4 Hz), 8.23 (d, 1H, J=6.8 Hz), 8.00 (d, 1H, J=8.1 Hz), 7.94 (t, 1H, J=7.0 Hz), 7.88 (t, 1H, J=7.6 Hz), 7.61 (d, 1H, J=7.8 Hz), 7.48–7.38 (m, 1H), 7.15 (t, 1H, J=6.5 Hz).

4.1.7. 2-Iodo-*N*-(6-methyl-pyridin-2-yl)-benzamide (1g). Yield: (92%); white crystalline solid; mp 101–103 °C. FT-IR (KBr): 3240, 2983, 1683, 1576, 1454, 1136, 1016, 798, 749 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm)=8.35 (br s, 1H, N*H*), 8.17 (d, 1H, J=8.1 Hz), 7.91 (d, 1H, J=8.0 Hz), 7.66 (t, 1H, J=7.8 Hz), 7.49 (d, 1H, J=7.5 Hz), 7.40 (t, 1H, J=7.5 Hz), 7.14 (t, 1H, J=7.7 Hz), 6.93 (d, 1H, J=7.5 Hz), 2.45 (s, 3H). Anal. Calcd for $C_{13}H_{11}N_2OI$: C, 46.17; H, 3.27; N, 8.28. Found: C, 46.15; H, 3.30; N, 8.30.

4.1.8. *N*-(1*R*-Hydroxymethyl-propyl)-2-iodo-benzamide (7). Yield: (94%); off-white solid; mp 106–108 °C. FT-IR (KBr): 3264, 2962, 1644, 1540, 1042, 725 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm)=7.77 (d, 1H, J=7.8 Hz), 7.35–7.27 (m, 2H), 7.05–6.99 (m, 1H), 5.90 (d, 1H, J=7.8 Hz, N*H*), 4.03–3.98 (m, 1H), 3.77 (dd, 1H, J=3.5,

3.5 Hz), 3.65 (dd, 1H, J=5.1, 5.1 Hz), 2.40 (br s, 1H, OH), 1.71–1.51 (m, 2H), 0.98 (t, 3H, J=7.4 Hz). Anal. Calcd for $C_{11}H_{14}NO_2I$: C, 41.39; H, 4.42; N, 4.38. Found: C, 41.35; H, 4.45; N, 4.40.

4.1.9. *N*-(1*R*-Phenyl-ethyl)-2-iodo-benzamide (8). Yield: (96%); off-white solid; mp 85–87 °C. FT-IR (KBr): 3299, 1640, 1529, 1447, 1317, 1014, 873, 743, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm)=7.84 (d, 1H, J= 7.8 Hz), 7.44–7.25 (m, 7H), 7.10–7.05 (m, 1H), 6.00 (br s, 1H, N*H*), 5.34 (p, 1H, J=7.3 Hz), 1.64 (d, 3H, J=6.9 Hz). Anal. Calcd for $C_{15}H_{14}NOI$: C, 51.29; H, 4.01; N, 3.98. Found: C, 51.26; H, 4.10; N, 4.00.

4.2. 5*H*-Phenanthridin-6-one (2) and biphenyl-2,2′-dicarboxylic acid bis-phenylamide (3a)

In a typical reaction procedure, a mixture of 2-iodo-*N*-phenyl-benzamide **1a** (340 mg, 1.05 mmol), $Pd(PPh_3)_2Cl_2$ (12 mg, 0.015 mmol), CuI (2.85 mg, 0.015 mmol), Et_3N (0.5 ml) and dry DMF (5.0 ml) was stirred at 120 °C for 12 h under nitrogen atmosphere. DMF was then distilled off, methylene chloride was then added and filtered through a pad of celite (3–4 cm). The organic layer was washed well with water followed by brine and then dried (Na_2SO_4). Removal of solvent followed by column chromatography furnished white solid **2** (30 mg, 15%) followed by **3a** (60 mg, 58%) as white crystalline solid.

4.2.1. 5*H*-Phenanthridin-6-one (2). Mp 198 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm)=9.46 (bs, 1H), 7.75–7.08 (m, 8H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=169.5, 138.16, 132.27, 132.07, 130.19, 129.80, 128.93, 128.74, 128.50, 128.15, 127.38, 124.47, 120.09. MS (EI): m/z (%)=195.1 (M^+, 14%), 122.1 (70%), 106.1 (100%). Anal. Calcd for $C_{13}H_9NO$: C, 79.98; H, 4.65; N, 7.17. Found: C, 79.96; H, 4.64; N, 7.15.

4.2.2. Biphenyl-2,2′-dicarboxylic acid bis-phenylamide (3a). Mp 228–229 °C [lit.[15] 229–230 °C]. UV/vis ($CHCl_3$): λ_{max} (log ε)=258 nm (8.7). FT-IR (KBr): 3444, 3251, 1644, 1540, 1488, 1321, 776 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm)=8.81 (bs, 2H), 7.26 (d, 2H, J=8.6 Hz), 7.36–7.31 (m, 8H), 7.19 (t, 4H, J=7.8 Hz), 7.12 (d, 2H, J=8.5 Hz), 7.00 (t, 2H, J=7.3 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm)=168.75, 139.51, 138.35, 136.53, 130.58, 130.13, 129.30, 128.52, 127.62, 124.88, 120.40. MS (EI): m/z (%)= 392.1 (M^+, 34%), 271.9 (31%), 181 (100%), 28 (75%). Anal. Calcd for $C_{26}H_{20}N_2O_2$: C, 79.59; H, 5.10; N, 7.14. Found: C, 79.55; H, 5.14; N, 7.23.

4.3. Synthesis of biphenyl-2,2′-dicarboxylic acid bis-phenylamide (3a). A general representative reaction procedure for symmetrical biaryls

A mixture of 2-iodo-*N*-phenyl-benzamide **1a** (120 mg, 0.37 mmol), $Pd(OAc)_2$ (3.36 mg, 0.015 mmol), CuI (2.85 mg, 0.015 mmol), Ph_3P (10 mg, 0.03 mmol), Et_3N (0.25 ml) and CH_3CN (5.0 ml) was stirred at 82 °C for 6 h under nitrogen atmosphere. The reaction mixture was then evaporated to dryness, CH_2Cl_2 was added and filtered through a pad of celite (3–4 cm). The organic layer was washed well with water followed by brine and then dried (Na_2SO_4). Removal of solvent followed by column chromatography afforded the white crystalline solid **3a** (25 mg, 70%) identical in all respects with the material described above. This protocol was successfully applied for other iodoarylbenzamides **1b–g** and for chiral **7** and **8**.

4.3.1. *N*-Butyryl-2-iodo-*N*-phenyl-benzamide (1a′). A mixture of 2-iodo-*N*-phenyl-benzamide **1a** (324 mg, 1 mmol), butyryl chloride (0.114 ml, 1.1 mmol) and Et_3N (0.153 ml, 1.1 mmol) in dry benzene was refluxed for 24 h under N_2 atmosphere. The product was purified by silica gel chromatography [CH_2Cl_2 and pet-ether (1:1)] to afford the butyryl protected derivative **1a′** as a cream-colored semi solid.

FT-IR (KBr): 3446, 2360, 1698, 1299, 696 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm)=7.68 (d, 1H, J=8.1 Hz), 7.34–7.17 (m, 7H), 6.95 (m, 1H), 2.51 (t, 2H, J=5.6 Hz), 1.65–1.52 (m, 2H), 0.84 (t, 3H, J=7.4 Hz). Anal. Calcd for $C_{17}H_{16}NO_2I$: C, 51.91; H, 4.10; N, 3.56. Found: C, 51.90; H, 4.12; N, 3.60.

4.4. Palladium catalyzed coupling of butyryl protected derivative (1a′)

A mixture of butyryl protected derivative **1a′** (100 mg, 0.264 mmol), $Pd(OAc)_2$ (2.97 mg, 0.0132 mmol), (o-tol)$_3$P (4.02 mg, 0.0132 mmol) and Na_2CO_3 (23.34 mg) in dry DMF (5.0 ml) was stirred at 150 °C for 1.5 h under nitrogen atmosphere. The reaction mixture was then evaporated to dryness, CH_2Cl_2 was added and filtered through a pad of celite (3–4 cm). After usual work-up and purifications, **3a** was isolated as a white crystalline solid (31 mg, 60%) identical in all respects with the above.

4.4.1. Biphenyl-2,2′-dicarboxylic acid bis-*o*-tolylamide (3b). Cream colored solid; mp 230–232 °C [lit.[16] 236 °C]. UV/vis ($CHCl_3$): λ_{max} (log ε)=247 nm (8.4). FT-IR (KBr): 3434, 2922, 1644, 1527, 1458, 1317, 1059, 757 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm)=8.35 (bs, 2H), 6.63 (d, 2H, J=8.8 Hz), 7.40–7.37 (m, 4H), 7.34 (d, 2H, J=7.9 Hz), 7.22 (d, 2H, J=8.7 Hz), 7.04 (t, 4H, J=6.5 Hz), 6.98 (t, 2H, J=7.0 Hz), 1.99 (s, 6H). MS (EI): m/z (%)=420 (M^+, 30%), 286 (25%), 181 (100%), 91 (28%). Anal. Calcd for $C_{28}H_{24}N_2O_2$: C, 79.98; H, 5.75; N, 6.66. Found: C, 80.00; H, 5.74; N, 6.70.

4.4.2. Biphenyl-2,2′-dicarboxylic acid bis-*m*-tolylamide (3c). White crystalline solid; mp 208–210 °C. UV/vis ($CHCl_3$): λ_{max} (log ε)=256 nm (10.7). FT-IR (KBr): 3443, 3264, 2925, 1645, 1598, 1550, 1440, 1331, 755 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm)=8.68 (bs, 2H), 7.62 (d, 2H, J=8.5 Hz), 7.36–7.31 (m, 4H), 7.24 (s, 2H), 7.13 (d, 2H, J=8.5 Hz), 7.10–7.05 (m, 4H), 6.82 (d, 2H, J=6.9 Hz), 2.24 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm)=168.70, 139.52, 139.22, 138.29, 136.62, 130.53, 130.12, 129.08, 128.48, 127.63, 125.69, 121.03, 117.54, 21.87. MS (EI): m/z (%)=420.4 (M^+, 40%), 286.2 (35%), 181 (100%), 116 (41%). Anal. Calcd for $C_{28}H_{24}N_2O_2$: C, 79.98; H, 5.75; N, 6.66. Found: C, 79.95; H, 5.76; N, 6.68.

4.4.3. Biphenyl-2,2′-dicarboxylic acid bis-[(4-methoxy-phenyl)-amide] (3d). White solid; mp 120–122 °C. UV/vis

($CHCl_3$): λ_{max} (log ε)=239 nm (10.1). FT-IR (KBr): 3307, 2955, 1650, 1512, 1232, 824, 741 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm)=8.82 (bs, 2H), 7.60 (d, 2H, J=8.6 Hz), 7.32–7.30 (m, 4H), 7.22 (d, 4H, J=6.9 Hz), 7.10 (d, 2H, J=6.4 Hz), 6.71 (d, 4H, J=6.9 Hz), 3.67 (s, 6H). MS (EI): m/z (%)=452.0 (M^+, 40%), 330 (30%), 181 (100%), 123 (85%). Anal. Calcd for $C_{28}H_{24}N_2O_4$: C, 74.32; H, 5.35; N, 6.19. Found: C, 74.30; H, 5.38; N, 6.22.

4.4.4. Biphenyl-2,2′-dicarboxylic acid bis-[(4-bezoic acid ethyl ester)-amide] (3e). Light yellow gum. UV/vis ($CHCl_3$): λ_{max} (log ε)=237 nm (7.7). FT-IR (KBr): 2980, 2940, 1655, 1540, 1435, 1390, 1295, 1100, 770, 710, 565 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm)=8.09 (br s, 2H), 7.73–7.28 (m, 16H), 3.39 (q, 2H, J=7.1 Hz), 3.30 (q, 2H, J=7.1 Hz), 1.18 (t, 3H, J=7.1 Hz), 1.12 (t, 3H, J=7.1 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm)=168.82, 168.51, 139.52, 138.29, 136.62, 125.69, 133.81, 133.46, 132.54, 130.65, 128.76, 126.09, 43.43, 14.71. MS (EI): m/z (%)=536.0 (M^+, 20%), 330 (30%), 181 (100%). Anal. Calcd for $C_{32}H_{28}N_2O_6$: C, 71.62; H, 5.25; N, 5.22. Found: C, 71.54; H, 5.28; N, 5.34.

4.4.5. Biphenyl-2,2′-dicarboxylic acid bis-pyridin-2-yl-amide (3f). Light yellow gum. UV/vis ($CHCl_3$): λ_{max} (log ε)=280 (8.5), 238 nm (9.3). FT-IR (KBr): 3450, 3085, 1690, 1610, 1580, 1550, 1460, 1400, 1310, 1240, 790, 755, 565 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm)=8.03 (bs, 2H), 7.92–7.80 (m, 4H), 7.46–7.35 (m, 4H), 7.21–7.02 (m, 8H). MS (EI): m/z (%)=366.4 (M^+, 40%), 234 (100%). Anal. Calcd for $C_{24}H_{18}N_4O_2$: C, 73.08; H, 4.60; N, 14.20. Found: C, 73.00; H, 4.58; N, 14.24.

4.4.6. Biphenyl-2,2′-dicarboxylic acid bis-[(6-methyl-pyridin-2-yl)-amide] (3g). Light brown solid; mp 176–178 °C (decomp). UV/cis ($CHCl_3$): λ_{max} (log ε)=285 (9.6), 240 nm (10.0). FT-IR (KBr): 3450, 3080, 1690, 1610, 1580, 1540, 1460, 1400, 1310, 1240, 790, 755, 715, 565 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm)=8.97 (bs, 2H), 7.92 (d, 2H, J=8.0 Hz), 7.70–7.68 (m, 2H), 7.53–7.38 (m, 6H), 7.24–7.21 (m, 2H), 6.80 (d, 2H, J=7.4 Hz), 2.36 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm)=168.52, 156.96, 150.93, 139.74, 139.02, 136.04, 130.87, 130.40, 128.39, 127.75, 119.70, 111.46, 22.90. MS (FAB): m/z (%)=423.3 (MH^+, 100%). Anal. Calcd for $C_{26}H_{22}N_4O_2$: C, 73.92; H, 5.25; N, 13.26. Found: C, 73.90; H, 5.30; N, 13.30.

4.4.7. Biphenyl-2,2′-dicarboxylic acid bis-[(1*R*-hydroxy-methyl-propyl)-amide] (5). Light brown semi solid. UV/vis ($CHCl_3$): λ_{max} (log ε)=259 (7.8), 239 nm (8.2). FT-IR (KBr): 3433, 2922, 2360, 1640, 1438, 1119, 722 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm)=7.67–7.63 (m, 4H), 7.55–7.41 (m, 4H), 6.50–6.44 (m, 2H, 2×N*H* amide), 4.52–4.48 (m, 1H), 4.23–4.19 (m, 1H), 4.01 (br s, 2H, OH), 3.75–3.71 (m, 2H), 3.68–3.65 (m, 2H), 1.87–84 (m, 2H), 1.70–1.63 (m, 2H), 1.07 (t, 3H, J=4.9 Hz), 0.99 (t, 3H, J=7.4 Hz). MS (EI): m/z (%)=384 (M^+, 20%), 330 (20%), 290 (40%), 249 (80%), 231 (100%), 105 (95%). Anal. Calcd for $C_{22}H_{28}N_2O_4$: C, 68.72; H, 7.34; N, 7.28. Found: C, 68.68; H, 7.38; N, 7.38.

4.4.8. Biphenyl-2,2′-dicarboxylic acid bis-[(1*R*-phenyl-ethyl)-amide] (6). White crystalline solid; mp 140–142 °C. $[\alpha]_D^{34}$=+28.50 (c 0.66, $CHCl_3$). UV/vis ($CHCl_3$): λ_{max} (log ε)=239 nm (10.9). FT-IR (KBr): 3090, 2980, 1620, 1505, 1460, 1220, 1190, 1130, 1100, 1080, 1030, 1000, 750, 725, 540 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm)=7.55–7.07 (m, 18H), 6.94 (br s, 2H), 5.02 (br s, 2H), 1.36 (d, 3H, J=11.3 Hz), 1.14 (d, 3H, J=11.0 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm)=169.35, 143.34, 139.40, 136.86, 136.53, 129.90, 129.82, 128.88, 128.84, 128.19, 128.14, 127.56, 127.34, 126.59, 126.46, 49.51, 49.19, 22.18, 21.74. MS (FAB): m/z (%)=449.6 (MH^+, 90%), 471.5 (100%). Anal. Calcd for $C_{30}H_{30}N_2O_2$: C, 79.96; H, 6.71; N, 7.10. Found: C, 79.92; H, 6.82; N, 7.21.

4.4.9. 3,3′-Bipyridyl-6,6′-dipivaloylamide (9). Off-white solid; mp 167–169 °C. UV/vis ($CHCl_3$): λ_{max} (log ε)=298 nm (9.9). FT-IR (KBr): 3434, 2953, 2360, 1671, 1503, 1314, 1166, 827 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm)=8.46 (d, 2H, J=2.31 Hz), 8.34 (d, 2H, J=8.76 Hz), 8.08 (bs, 2H), 7.88 (dd, 2H, J=8.66 Hz), 1.35 (s, 18H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm)=177.51, 151.51, 145.91, 136.81, 129.67, 114.27, 40.24, 27.87. HRMS (FAB): m/z calculated for $C_{20}H_{26}N_4O_2$ $(M+Na)^+$: 377.1953; Found: 377.1952.

4.4.10. 6,6′-Dimethyl-2,2′-bipyridyl (10). Cream colored solid; mp 82–85 °C (lit.[17] 89–90 °C).

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11. *Crystallographic data* **3a**: Chemical formula $C_{26}H_{20}N_2O_2$, Molecular weight 392.44 g mol^{-1}, tetragonal, space group $P4_32_12$ (No. 96), $a=b=10.7822(9)$, $c=35.902(4)$ Å, $\alpha=\beta=\gamma=90°$, $V=4173.8(6)$ Å^3, $Z=8$, $T=294(2)$ K, density = 1.249 g cm^{-3} (calc.), $F(000)=1648$, $\mu=0.080$ cm^{-1}, 5203 reflections from 2–25°, 2235 unique (1342 with $I>2\sigma I$), 272 parameters, R-factor is 0.066, $wR_2=0.126$ [based on F^2 for reflections with $I>2\sigma I$)], $Gof=1.04$, density range in final Δ-map is -0.29 to $+0.28$ e.A^{-3}, (solved in SHELXL97, refined in SHELXL97). *Crystallographic data* **6**: Chemical formula $C_{31}H_{29}N_2O_2Cl_3$ (as chloroform solvate): Molecular weight 567.91 g mol^{-1}, orthorhombic, space group $P2_12_12_1$ (No. 19), $a=11.7763(7)$, $b=14.4974(12)$, $c=17.4072(17)$ Å, $\alpha=\beta=\gamma=90°$, $V=2971.9(4)$ Å^3, $Z=4$, $T=294(2)$ K, density = 1.269 g cm^{-3} (calc.), $F(000)=1148$, $\mu=0.338$ cm^{-1}, 5950 reflections from 2 to 25°, 5275 unique (3850 with $I>2\sigma I$), 346 parameters, R-factor is 0.043, $wR_2=0.078$ [based on F^2 for reflections with $I>2\sigma I$)], $Gof=1.03$, density range in final Δ-map is -0.20 to $+0.20$ e.A^{-3}, (solved in SHELXL97, refined in SHELXL97). The crystallographic data for **3a** and **6** have been deposited with the Cambridge Crystallographic Data Centre, CCDC as No. 190491 and 209565. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).
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Synthetic studies on 3-arylquinazolin-4-ones: intramolecular nucleophilic aromatic substitution reaction of 2-carboxamido-3-arylquinazolin-4-ones and its application to the synthesis of secondary aryl amines

Haruhiko Fuwa, Toshitake Kobayashi,† Takashi Tokitoh, Yukiko Torii and Hideaki Natsugari*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

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Abstract—The general synthesis and a novel intramolecular nucleophilic aromatic substitution (S_NAr) reaction of 2-carboxamido-3-arylquinazolin-4-ones, a potentially useful scaffold in the field of medicinal chemistry, are described. The synthetic utility of the S_NAr reaction as a tool for the synthesis of secondary aryl amines, including diaryl amines, is also demonstrated.

1. Introduction

3-Arylquinazolin-4-one has been extensively utilized as a core structure in the field of medicinal chemistry, as represented by methaqualone and its related derivatives (Fig. 1).[1] For example, researchers from Pfizer have recently discovered a novel potent AMPA receptor antagonist CP-465,022 based on 3-(2-chlorophenyl)-6-fluoroquinazolin-4-one as the template.[2] It should be noted that CP-465,022 exists as a separable mixture of atropisomers and its anticonvulsant activity resides in only one of the atropisomers [i.e., (+)-CP-465,022]. The relationship between the atropisomeric property and biological activity makes 3-arylquinazolin-4-one an intriguing structure. The 3-arylquinazolin-4-one motif can also be found in natural products, as exemplified by benzomalvin A,[3] circumdatin F[4] and tryptanthrin.[5] Thus, 3-arylquinazolin-4-one is an important and potentially useful structural motif for the design and synthesis of biologically active molecules.[6] Here we describe in detail the synthesis of 2-carboxamido-3-arylquinazolin-4-ones and their intramolecular nucleophilic aromatic substitution (S_NAr) reaction. Application of the intramolecular S_NAr reaction to the synthesis of secondary aryl amines, including diaryl amines, is also described.[7]

2. Results and discussion

2.1. Synthesis of 2-carboxamido-3-arylquinazolin-4-ones

As a part of our synthetic studies on 3-arylquinazolin-4-ones for the development of biologically active molecules, we designed and targeted the 2-carboxamido-3-arylquinazolin-4-ones (e.g., **10** and **12**–**16**), and the general synthesis was investigated starting from 2-ethoxycarbonyl-3-arylquinazolin-4-ones (**9a**–**g**) as the key intermediates (Scheme 1). The synthesis of **9a**–**g** commenced with the acylation of the aromatic amines **6a**–**g** ($ClCOCO_2Et$, pyridine) to obtain the oxalamic acid esters **7a**–**g** (Scheme 1), which were then subjected to dehydrative cyclization to form **9a**–**g** using the following two methods. The first (Method A) is that used for the synthesis of several natural quinazoline alkaloids:[8,9] compounds **7a**–**g** were treated with I_2, PPh_3 and *i*-Pr_2NEt at room temperature to give a mixture of the iminobenzoxadines **8a**–**g** and quinazolin-4-ones **9a**–**g**, which, without separation, were treated with pyrrolidine in AcOH/THF (1:10) under refluxing conditions to provide the desired 3-arylquinazolin-4-ones **9a**–**g** in moderate to good overall yields. However, this method requires tedious chromatographic separation of the desired products (i.e., iminobenzoxazine and quinazolin-4-one) from the co-product triphenylphosphine oxide and excess triphenylphosphine, which makes this protocol less attractive particularly in the

Keywords: Quinazolinone; 2-Carboxamido-3-arylquinazolin-4-one; Nucleophilic aromatic substitution; Intramolecular reaction; Secondary aryl amine.
* Corresponding author. Tel./fax: +81 3 5841 4775;
e-mail: natsu@mol.f.u-tokyo.ac.jp
† On leave from Takeda Pharmaceutical Company Limited. Present address: Medicinal Chemistry Research Laboratories, Pharmaceutical Research Division, Takeda Pharmaceutical Company Limited, 10 Wadai, Tsukuba, Ibaraki 300-4293, Japan.

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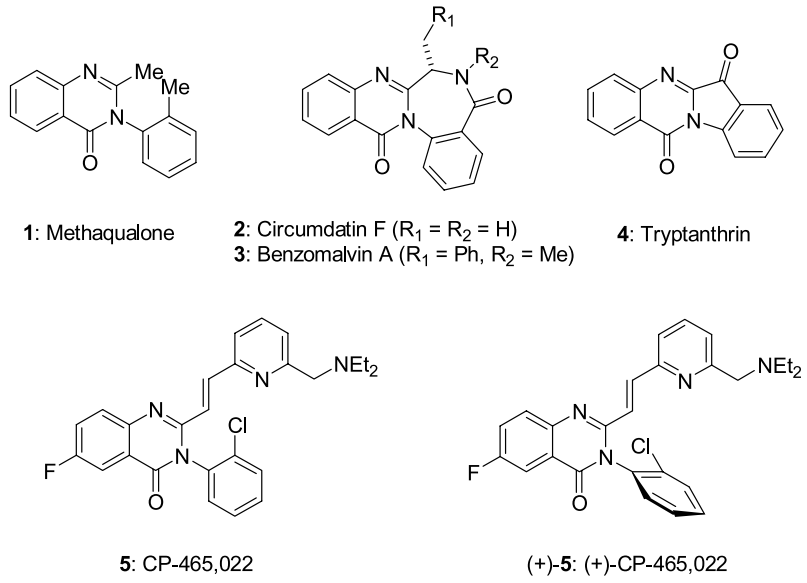
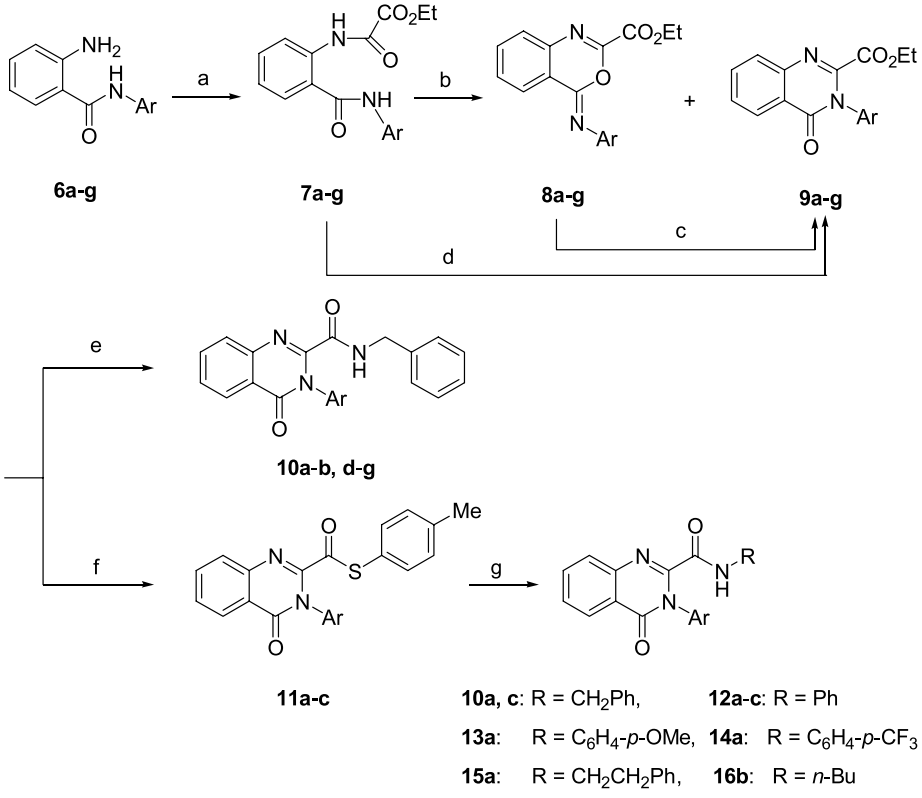
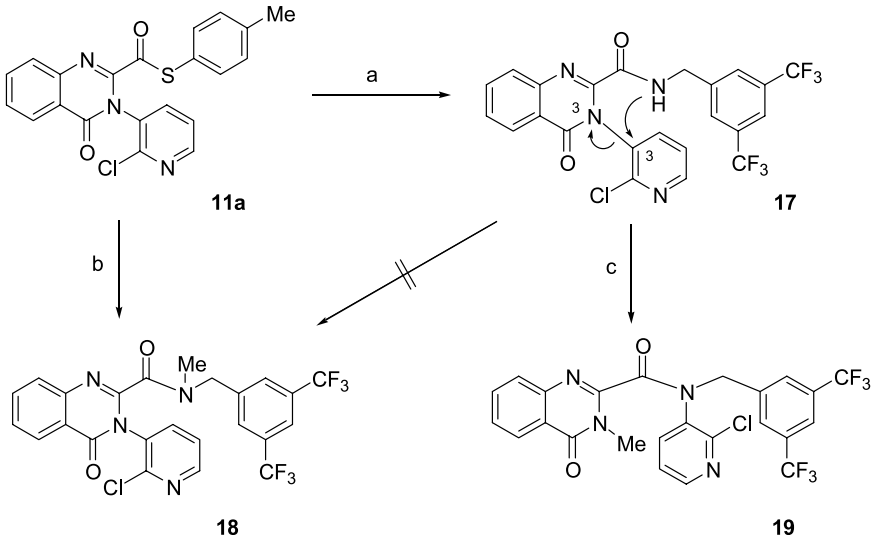


Figure 1. Representative biologically active molecules that possess the 3-arylquinazolin-4-one structural motif.



Scheme 1. Synthesis of 2-carboxamido-3-(2-chloro-3-pyridyl)quinazolin-4-ones. Reagents and conditions: (a) $ClCOCO_2Et$ (1.2 equiv), pyridine (1.5 equiv), THF, 0 °C, 90–98%; (b) I_2 (3 equiv), PPh_3 (3 equiv) *i*-Pr_2NEt (10 equiv), CH_2Cl_2, 0 °C to rt; (c) pyrrolidine (1.2 equiv), THF/AcOH (10:1), reflux, 46–94% (2 steps); (d) TMSCl (15 equiv), Et_3N (46 equiv), $ClCH_2CH_2Cl$, 40 mM, 80 °C, 84–100%; (e) $AlMe_3$ (4 equiv) $PhCH_2NH_2$ (4 equiv), CH_2Cl_2, 0 °C to rt, 53–100%; (f) *p*-MeC_6H_5SH (4 equiv), $AlMe_3$ (4 equiv), CH_2Cl_2, 0 °C to rt, 60–91%; (g) RNH_2 (3 equiv), $AgOCOCF_3$ (1.1 equiv), THF/toluene (1:1), 60 °C, 81–100%.

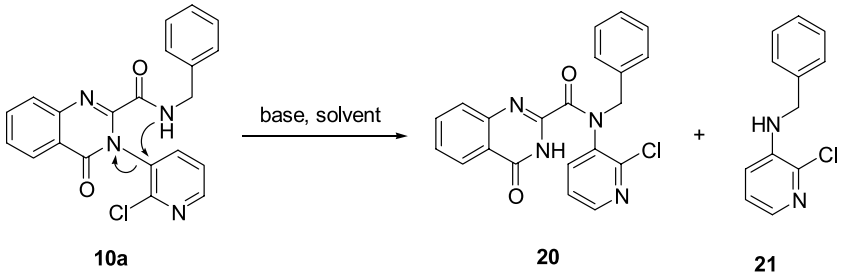


Scheme 2. Reagents and conditions: (a) 3,5-bis(trifluoromethyl)benzylamine (3 equiv), $AgOCOCF_3$ (1.1 equiv), THF/toluene (1:1), 60 °C, 100%; (b) *N*-[3,5-bis(trifluoromethyl)]-*N*-methylbenzylamine (3 equiv), $AgOCOCF_3$ (1.1 equiv), THF/toluene (1:1), 60 °C, 100%; (c) NaH (1.2 equiv), DMF, 0 °C to rt, then MeI (10 equiv), 0 °C to rt, 81%.

case of large-scale synthesis. The second method (Method B) is based on the protocol appearing in a patent literature,[10] in which several quinazolin-4-ones were prepared by dehydration of 2-carbamoylanilides using trimethylsilyl chloride (TMSCl) in the presence of Et_3N. Using the modified conditions (**7a–g**, TMSCl, Et_3N in 1,2-dichloroethane at 80 °C), the desired 2-ethoxycarbonyl-3-arylquinazolin-4-ones **9a–g** were directly obtained in excellent yields. Two points in the present cyclodehydration process should be noted. The concentration at which the reaction is performed (ca. 40 mM) is important for the clean conversion. Further, the reaction temperature is also an important factor: when the reaction was performed at 40 °C the rate of the reaction was very slow, and at higher temperature (>100 °C) the yields of **9a–g** were significantly reduced.

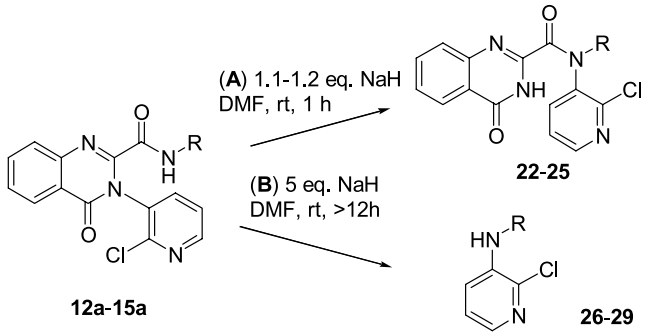
Conversion of the ethyl esters **9a–g** to the corresponding amide derivatives was found not to be trivial because the corresponding carboxylic acids readily underwent decarboxylation.[11] Therefore, we were forced to employ an amidation method that does not require hydrolysis of the ethyl esters **9a–g**. The benzylamide **10a** could be quantitatively produced using dimethylaluminum amide method ($PhCH_2NH_2$, $AlMe_3$).[12] The other benzylamide derivatives **10b** and **10d–g** could also be synthesized in the same manner. In the case of aromatic amines, however, the desired amides could not be obtained reproducibly, presumably due to their low nucleophilicity. After several unfruitful attempts, we reached a general solution for this chemical transformation. Thus, the ethyl esters **9a–c** were first converted to the *p*-tolylthiol esters **11a–c** by the action of sufficiently reactive dimethylaluminum thiolate $Me_2AlSC_6H_4$-*p*-Me (generated in situ from Me_3Al and *p*-MeC_6H_4SH),[13] which were then reacted with an appropriate primary amine in the presence of $AgOCOCF_3$ [THF/toluene (1:1), 60 °C],[14] giving a series of 2-carboxamido-3-arylquinazolin-4-ones (**10a–c**, **12a–c**, **13a**, **14a**, **15a** and **16b**) in high yields. Thus, we have developed an efficient synthetic entry to 2-carboxamido-3-arylquinazolin-4-ones, which comprises the following steps: (i) acylation of aromatic amines **6a–g**, (ii) dehydrative cyclization by the action of TMSCl/Et_3N, (iii) conversion of the ethyl ester to the *p*-tolylthiol ester with $Me_2AlSC_6H_4$-*p*-Me and (iv) $AgOCOCF_3$-mediated amidation.

Table 1. Effects of solvent and molar amount of base on the intramolecular S_NAr reaction



Entry	Reagents and conditions	Product	Yield (%)
1	NaH (1.2 equiv), DMF, rt, 1 h	**20**	76
2	NaH (1.2 equiv), THF, rt, 2 h	**20**	75
3	NaH (3 equiv), toluene, 80 °C, overnight	**20**	85
4	NaH (5 equiv), DMF, rt, overnight	**21**	76

Table 2. Intramolecular S_NAr reaction of 2-carboxamido-3-(2-chloro-3-pyridyl)quinazolin-4-ones (**12a–15a**) (**A**) and synthesis of secondary aryl amines from **12a–15a** (**B**)



Entry	Substrate	R	(A)		(B)	
			Product	Yield (%)	Product	Yield (%)
1	**12a**	Ph	**22**	88	**26**	85
2	**13a**	C_6H_4-*p*-OMe	**23**	87	**27**	49
3	**14a**	C_6H_4-*p*-CF_3	**24**	100	**28**	84
4	**15a**	CH_2CH_2Ph	**25**	63	**29**	100

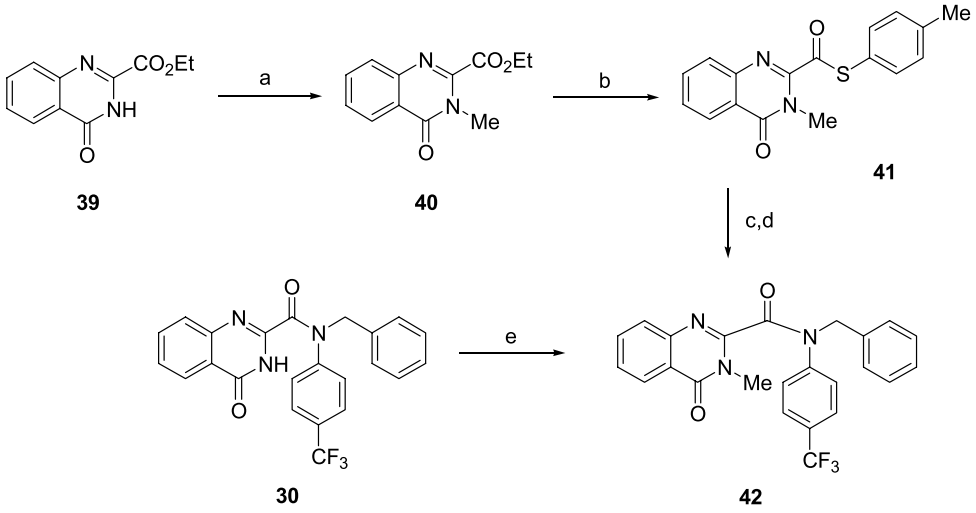
2.2. Intramolecular S_NAr reaction of 2-carboxamido-3-arylquinazolin-4-ones

Using the methodology described above, the 2-carboxamido-3-arylquinazolin-4-ones with *N*-[3,5-bis(trifluoromethyl)benzyl] groups, **17** and **18** (Scheme 2), which we had anticipated would possess NK_1 receptor antagonistic activity,[15] were prepared by treatment of **11a** with 3,5-bis(trifluoromethyl)benzylamine and *N*-[3,5-bis(trifluoromethyl)]-*N*-methylbenzylamine in the presence of $AgOCOCF_3$, respectively. To our surprise, treatment of **17** with NaH followed by the addition of MeI exclusively gave the migrated tertiary amide **19** instead of the expected *N*-methylated product **18**. The migration of the N3-pyridyl group was induced by the action of NaH, that is, the amide-nitrogen anion first formed attacked the C3 of the pyridine ring and then the C3–N3 bond was cleaved, resulting in the migration of the pyridyl group. Subsequent trapping of the resultant anion at the N3 of the quinazolinone ring with MeI furnished the migrated tertiary amide **19** (Scheme 2). This unique rearrangement is considered to fall into a category of the intramolecular S_NAr reaction. Intrigued by this unexpected and unprecedented result, we attempted to investigate the scope and limitation of the migration reaction of 2-carboxamido-3-arylquinazolin-4-ones.

We first examined the effects of the solvent and molar amount of base employing the benzyl amide **10a** as a model substrate (Table 1). Upon treatment of **10a** with NaH in DMF at room temperature for 1 h, the tertiary amide **20** was produced in 76% yield (entry 1 in Table 1). The reaction also proceeded smoothly in THF to yield **20**, but a slightly longer reaction time was required (entry 2). In contrast, using toluene as a solvent, heating of the reaction mixture and a prolonged reaction time were required for the reaction to be completed (entry 3). Surprisingly, exposure of **10a** to a fivefold molar excess of NaH in DMF at room temperature overnight resulted in in situ cleavage of **20**, giving rise to the secondary aryl amine **21** as the sole isolatable product after aqueous workup (entry 4). Since we performed the experiment with reagent-grade DMF under aerobic conditions, it was assumed that the unexpected production of **21**

Table 3. Effect of the substituent of the N3 aryl group

Entry	Substrate	X	R	Product	Yield (%)
1	**10b**	*p*-CF_3	CH_2Ph	**30**	95
2	**12b**	*p*-CF_3	Ph	**31**	85
3	**16b**	*p*-CF_3	*n*-Bu	**32**	100
4	**10c**	*o*-CO_2Me	CH_2Ph	**33**	100
5	**12c**	*o*-CO_2Me	Ph	**34**	72
6	**10d**	*p*-CN	CH_2Ph	**35**	95
7	**10e**	*m*-CF_3	CH_2Ph	**36**	0
8	**10f**	*p*-OMe	CH_2Ph	**37**	0
9	**10g**	H	CH_2Ph	**38**	0

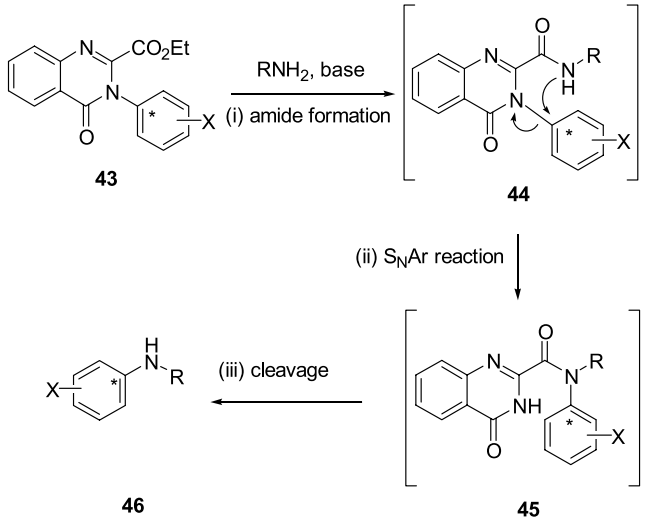


Scheme 3. Reagents and conditions: (a) MeI (5 equiv), NaHMDS (1.2 equiv), DMF, 0 °C to rt, 72%; (b) *p*-MeC_6H_4SH (4 equiv), $AlMe_3$ (4 equiv), CH_2Cl_2, 0 °C to rt, 71%; (c) *p*-(trifluoromethyl)aniline (3 equiv), $AgOCOCF_3$ (1.1 equiv), THF/toluene (1:1), 60 °C, 80%; (d) NaH (1.2 equiv), BnBr (1.5 equiv), DMF, 0 °C to rt, 99%; (e) NaH (1.2 equiv), MeI (10 equiv), DMF, 0 °C to rt, 92%.

could be ascribed to adventitious H_2O absorbed from moisture, generating dry NaOH that is sufficiently reactive to cleave the tertiary amide moiety of **20**.[16]

To validate the substrate scope of the present S_NAr reaction, a variety of 2-carboxamido-3-(2-chloro-3-pyridyl)quinazolin-4-ones (**12a**–**15a**) were examined as substrates (Table 2). Upon treatment of the quinazolin-4-ones **12a**–**15a** with 1.1–1.2 equiv of NaH in DMF at room temperature for 1 h, all compounds cleanly furnished the migrated products, that is, 2-*N*-(2-chloro-3-pyridyl)carboxamidoquinazolin-4-one derivatives (**22**–**25**) (Table 2A). On the other hand, when using 5 equiv of NaH (DMF, room temperature, overnight), all quinazolin-4-ones (**12a**–**15a**) delivered the respective secondary aryl amines (**26**–**29**) (Table 2B) in satisfactory yields. These results indicate that aliphatic, benzylic and aromatic amides can be employed in the present reaction.

We then investigated the effect of the substituent of the N3 aryl group as shown in Table 3. It was found that the reactions also proceeded with the N3 phenyl derivatives and that the presence of an electron withdrawing group(s) at the ortho or para position of the N3 phenyl group was essential for the success of the present reaction: *p*-CF_3 (**10b**, **12b** and **16b**), *o*-CO_2Me (**10c** and **12c**) and *p*-CN (**10d**) derivatives cleanly furnished the corresponding migrated tertiary amides [i.e., 2-(*N*-aryl)carboxamidoquinazolin-4-ones **30**–**35**] upon treatment with 1.2 equiv of NaH in DMF at room temperature. On the other hand, *m*-CF_3 (**10e**), *p*-OMe (**10f**) and unsubstituted (**10g**) derivatives did not participate in the present reaction. In these cases, attempts to migrate the N3 aryl group by extending the reaction time and/or forcing the reaction conditions only gave a mixture of several unidentified products. These results imply that the present reaction is based on an S_NAr mechanism.

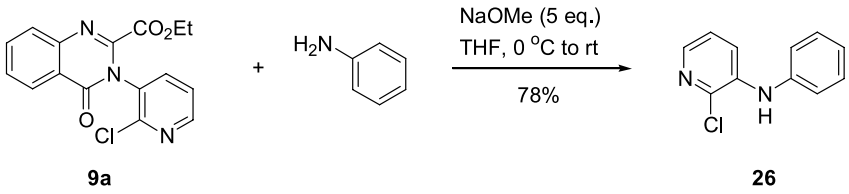


Scheme 4. A cascade process leading to the generation of the secondary aryl amines.

The structures of the migrated products were characterized on the basis of NMR, IR and HRMS spectra. Moreover, in the case of **30**, further structural confirmation was obtained by comparison of the spectroscopic data of the *N*-methylated product **42** with those of authentic sample prepared as described in Scheme 3. Thus, *N*-methylation of the known quinazolin-4-one **39**[11] with sodium bis(trimethylsilyl)amide (NaHMDS) and MeI gave **40**,[17] which was exposed to $Me_2AlSC_6H_4$-*p*-Me to give **41**. Amidation of **41** with 4-(trifluoromethyl)aniline in the presence of $AgOCOCF_3$ and the ensuing *N*-benzylation of the resultant amide (BnBr, NaH) furnished **42** in good overall yield. The spectroscopic properties of this material **42** were indistinguishable from those of the sample obtained from **30** through *N*-methylation (MeI, NaH), thereby unambiguously confirming the structure of **30**.

2.3. Expeditious synthesis of secondary aryl amines

Based on the above results, we surmised that a reaction of the 2-ethoxycarbonyl-3-arylquinazolin-4-ones (**9**) and primary amines in the presence of a base would induce a cascade process comprised of (i) amide formation (**43**→**44**), (ii) intramolecular S_NAr reaction (**44**→**45**) and (iii)

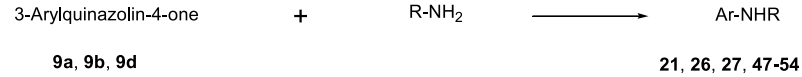


Scheme 5.

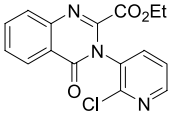
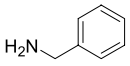
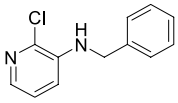
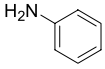
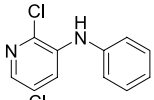
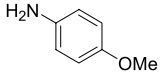
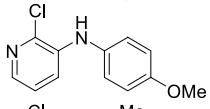
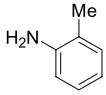
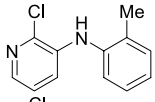
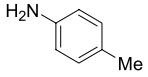
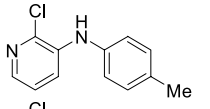
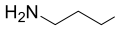
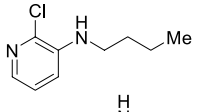
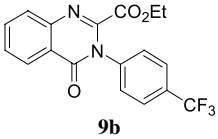
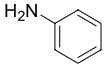
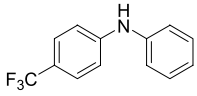
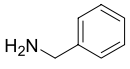
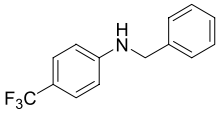
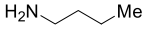
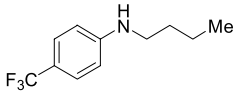
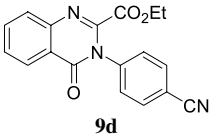
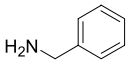
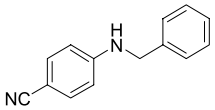
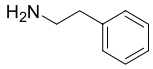
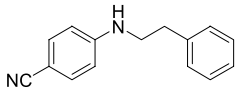
cleavage of the resultant tertiary amide (**45**→**46**), leading to the one-pot generation of secondary aryl amines (Scheme 4).

Consequently, we found that treatment of the ethyl ester **9a** with 1.5 equiv of aniline and 5 equiv of NaOMe in reagent-grade THF at room temperature under aerobic conditions gave the secondary aryl amine **26** in 78% yield (Scheme 5). It should be noted that the cleavage of the tertiary amide intermediate to produce the secondary aryl amine was

Table 4. Expeditious synthesis of secondary aryl amines[a]



9a, **9b**, **9d** — **21**, **26**, **27**, **47-54**

Entry	3-Arylquinazolin-4-one	R-NH_2	Product (Ar-NHR)	Yield (%)
1	 **9a**		 **21**	73
2	**9a**		 **26**	78
3	**9a**		 **27**	49
4	**9a**		 **47**	64
5	**9a**		 **48**	82
6	**9a**		 **49**	64
7	 **9b**		 **50**	59
8	**9b**		 **51**	77
9	**9b**		 **52**	71
10	 **9d**		 **53**	74
11	**9d**		 **54**	81

[a] All reactions were performed using 1.5 equiv of amine and 5 equiv of NaOMe in wet THF at room temperature.

dramatically enhanced by a small amount of H_2O contaminated in the reagent-grade THF.[16] The present cascade reaction was then applied to a series of substrates, and the results are summarized in Table 4. Various aliphatic, benzylic and aromatic amines could be employed in this process. It should be mentioned that the present method does not require strict inert anhydrous reaction conditions and is operationally very simple. It also offers easy access to diaryl amines (e.g., **26**, **27**, **47**, **48** and **50**) that are mainly synthesized via metal-catalyzed cross-coupling reactions.[18]

3. Conclusion

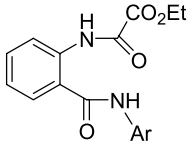
A general synthetic entry to 2-carboxamido-3-arylquinazolin-4-ones and the discovery of their intramolecular S_NAr reaction, which is rarely predictable from conventional heterocyclic chemistry, are described. The requirement for the success of the present migration reaction is the presence of an electron-withdrawing group on the N3 aryl ring, which is consistent with that of usual S_NAr reactions. The present reaction has been applied to the synthesis of secondary aryl amines, including diaryl amines, the notable feature of which is its operational simplicity.

4. Experimental

4.1. General remarks

All reactions sensitive to air and/or moisture were carried out under an atmosphere of argon in oven-dried glassware with anhydrous solvents unless otherwise noted. All anhydrous solvents and reagent grade *N*,*N*-dimethylformamide (DMF) and tetrahydrofuran (THF) were purchased from Wako Pure Chemicals Co. Inc. and used without further drying. All other reagents purchased were of the highest commercial quality and used as received unless otherwise stated. Analytical thin layer chromatography was carried out using E. Merck silica gel 60 F_{254} plates (0.25 mm thickness). Open column chromatography was performed on Kanto Chemical silica gel 60N (spherical, neutral). Flash chromatography was carried out using Fuji Silysia silica gel BW300 (200–400 mesh) or Fuji Silysia chromatorex–NH silica gel (100–200 mesh). Melting points were taken on a Yanagimoto micro melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were taken on a JEOL JNM-LA400 spectrometer in $CDCl_3$ unless otherwise noted. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane and coupling constants (*J*) are reported in hertz (Hz). Tetramethylsilane was defined as 0 ppm for ^1H NMR and the

Table 5. Physicochemical properties of *N*-(2-aryl-carbamoylphenyl)oxalamic acid ethyl esters (**7a**–**g**)



Compound	Ar	Yield (%)	Mp (°C)	^1H NMR (400 MHz, $CDCl_3$) δ	HRFABMS [(M+H)$^+$], calcd (found)
7a	2-Chloro-3-pyridyl	97	169–171	12.33 (br s, 1H), 8.90 (d, J=7.2 Hz, 1H), 8.77 (d, J=9.2 Hz, 1H), 8.47 (br s, 1H), 8.20 (m, 1H), 7.76 (d, J=7.2 Hz, 1H), 7.65 (t, J=7.2 Hz, 1H), 7.37–7.27 (m, 2H), 4.44 (q, J=7.2 Hz, 2H), 1.44 (t, J=7.2 Hz, 3H)	$C_{16}H_{15}ClN_3O_4$ 348.0751 (348.0739)
7b	–C_6H_4–*p*-CF_3	98	212	12.19 (br s, 1H), 8.64 (d, J=8.4 Hz, 1H), 8.15 (s, 1H), 7.80 (d, J=9.2 Hz, 2H), 7.66 (m, 3H), 7.57 (t, J=7.6 Hz, 1H), 7.23 (t, J=7.6 Hz, 1H), 4.44 (q, J=7.2 Hz, 2H), 1.44 (t, J=7.2 Hz, 3H)	$C_{18}H_{16}F_3N_2O_4$ 381.1062 (381.1046)
7c	–C_6H_4–*o*-CO_2Me	97	173–174	12.16 (br s, 1H), 8.91 (d, J=8.4 Hz, 1H), 8.76 (d, J=9.2 Hz, 1H), 8.09 (d, J=7.2 Hz, 1H), 7.94 (d, J=8.0 Hz, 1H), 7.67–7.57 (m, 2H), 7.31 (t, J=7.2 Hz, 1H), 7.16 (t, J=8.4 Hz, 1H), 4.44 (q, J=7.2 Hz, 2H), 3.97 (s, 3H), 1.45 (t, J=7.2 Hz, 3H)	$C_{19}H_{19}N_2O_6$ 438.1429 (438.1425)
7d	–C_6H_4–*p*-CN	91	195–197	12.13 (br s, 1H), 8.66 (d, J=9.2 Hz, 1H), 8.15 (br s, 1H), 7.82 (d, J=8.4 Hz, 2H), 7.72–7.63 (m, 3H), 7.58 (m, 1H), 7.23 (m, 1H), 4.44 (q, J=7.2 Hz, 2H), 1.44 (t, J=7.2 Hz, 3H)	$C_{18}H_{16}N_3O_4$ 338.1141 (338.1137)
7e	–C_6H_4–*m*-CF_3	98	159–160	(DMSO-d_6) 11.91 (br s, 1H), 10.83 (s, 1H), 8.38 (d, J=8.4 Hz, 1H), 8.20 (s, 1H), 8.01–7.90 (m, 2H), 7.68–7.59 (m, 2H), 7.50 (d, J=8.4 Hz, 1H), 7.35 (m, 1H), 4.29 (q, J=7.2 Hz, 2H), 1.30 (t, J=7.2 Hz, 3H)	$C_{18}H_{16}F_3N_2O_4$ 381.1062 (381.1060)
7f[26]	–C_6H_4–*p*-OMe	96	199–200 (lit.[26] 204–205)	12.39 (br s, 1H), 8.68 (d, J=8.4 Hz, 1H), 7.84 (br s, 1H), 7.66 (d, J=7.2 Hz, 1H), 7.59–7.46 (m, 3H), 7.22 (m, 1H), 6.92 (d, J=9.2 Hz, 2H), 4.42 (q, J=7.2 Hz, 2H), 3.83 (s, 3H), 1.43 (t, J=7.2 Hz, 3H)	$C_{18}H_{19}N_2O_5$ 343.1294 (343.1299)
7g[26]	–Ph	90	158–160 (lit.[26] 160–161)	(DMSO-d_6) 12.06 (br s, 1H), 10.57 (s, 1H), 8.42 (d, J=8.4 Hz, 1H), 7.93 (d, J=7.2 Hz, 1H), 7.73 (d, J=7.2 Hz, 2H), 7.62 (t, J=7.2 Hz, 1H), 7.43–7.27 (m, 3H), 7.14 (t, J=7.2 Hz, 1H), 4.29 (q, J=7.2 Hz, 2H), 1.29 (t, J=7.2 Hz, 3H)	$C_{17}H_{17}N_2O_4$ 313.1188 (313.1188)

center line of the triplet of $CDCl_3$ was also defined as 77.0 ppm for ^{13}C NMR. The following abbreviations are used to designate the multipilicities: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Low- and high-resolution mass spectra were recorded on a JEOL SX-102A mass spectrometer under fast atom bombardment (FAB) conditions using *m*-nitrobenzyl alcohol (NBA) as a matrix. Extracted solutions were dried over anhydrous $MgSO_4$ or anhydrous Na_2SO_4, and solvents were evaporated under reduced pressure.

4.2. Synthesis of 3-aryl-3,4-dihydro-4-oxo-2-quinazolinecarboxylic acid ethyl esters (10a–g, 12a–c, 13a, 14a, 15a, 16b, 17)

4.2.1. *N*-(2-Aryl-carbamoylphenyl)oxalamic acid ethyl esters (7a–g). As a typical example, the preparation of *N*-[2-(2-chloro-3-pyridyl)carbamoylphenyl]oxalamic acid ethyl ester (**7a**) is described. To a solution of aromatic amine **6a**[19] (0.50 g, 2.02 mmol) in THF (10 mL) at 0 °C were added pyridine (0.190 mL, 2.34 mmol) and $ClCOCO_2Et$ (0.270 mL, 2.42 mmol). After being stirred at 0 °C for 15 min, the mixture was concentrated. To the concentrate were added EtOAc and H_2O, and the organic layer was separated. The aqueous layer was extracted with EtOAc. The organic layers were combined, washed with brine, dried, and concentrated to give a pale yellow solid. Crystallization from *i*-Pr_2O gave **7a** (0.68 g, 97%) as pale yellow crystals. The physicochemical properties are described in Table 5.

Similarly, **7b**–**g** were prepared from the known aromatic amines **6b**–**g** (**6b**,[20] **6c**,[21] **6d**,[22] **6e**,[23] **6f**,[24] and **6g**[25]). The physicochemical properties are listed in Table 5.

4.2.2. 3-Aryl-3,4-dihydro-4-oxo-2-quinazolinecarboxylic acid ethyl esters (9a–g). Two methods (Method A and B) were used for the preparation of **9a**–**g**. As a typical example, the preparation of 3-(2-chloro-3-pyridyl)-3,4-dihydro-4-oxo-2-quinazolinecarboxylic acid ethyl ester (**9a**) is described.

Method A. To a solution of **7a** (9.50 g, 27.4 mmol) in CH_2Cl_2 (100 mL) cooled at 0 °C were sequentially added *i*-Pr_2NEt (48.0 mL, 276 mmol), PPh_3 (21.6 g, 82.4 mmol) and I_2 (20.9 g, 82 mmol). The mixture was stirred at room temperature for 50 min and then diluted with EtOAc. The organic layer was washed with 10% aqueous Na_2CO_3 and brine, dried, and concentrated. Purification of the residue by open column chromatography (silica gel, 40% EtOAc/hexane) gave a mixture of iminobenzoxazine **8a** and quinazolin-4-one **9a** (10.8 g), which was used in the next reaction without separation.

To a solution of the above mixture in THF (200 mL) were added pyrrolidine (2.80 mL, 33.5 mmol) and AcOH (20 mL). The mixture was heated under reflux for 1 h, cooled to room temperature, and concentrated. The residue was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. Purification of the residue by open column chromatography (silica gel, 40% EtOAc/hexane) gave **9a** (8.20 g, 94% for the two steps). Crystallization from *i*-Pr_2O gave **9a** as colorless crystals. The physicochemical properties are described in Table 6.

Method B. The following reaction was carried out under an atmosphere of argon. To a solution of **7a** (347 mg, 1.00 mmol) in $ClCH_2CH_2Cl$ (25 mL) were added Et_3N (6.43 mL, 46.0 mmol) and TMSCl (1.90 mL, 15.0 mmol). The mixture was heated under gentle reflux for 1.5 h. After cooling, the mixture was diluted with EtOAc, washed successively with 1 M aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. Purification of the residue by flash chromatography (silica gel, BW300, 50% EtOAc/hexane) gave **9a** as colorless crystals (329 mg, 100%). The physicochemical data were identical with those of **9a** prepared by Method A. Similarly, **9b**–**g** were prepared from **7b**–**g** by Method A and B. The physicochemical properties are listed in Table 6.

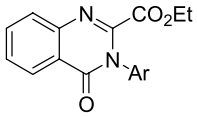
4.3. 3-Aryl-3,4-dihydro-4-oxo-2-quinazolinecarboxamides (10a–g, 12a–c, 13a, 14a, 15a, 16b, 17)

Two methods (Method A and/or B) were used for the preparation of 3-aryl-3,4-dihydro-4-oxo-2-quinazolinecarboxamides. As the typical examples, the syntheses of *N*-benzyl-3-(2-chloro-3-pyridyl)-3,4-dihydro-4-oxo-2-quinazolinecarboxamide (**10a**) by Method A and B are described.

4.3.1. Method A. The following reaction was carried out under an atmosphere of argon. To a solution of benzylamine (0.220 mL, 2.01 mmol) in CH_2Cl_2 (5 mL) cooled at 0 °C was added a solution of $AlMe_3$ (1.0 M solution in hexane, 2.00 mL, 2.00 mmol). The mixture was stirred at room temperature for 1 h and then cooled to 0 °C. To this solution was added quinazolin-4-one **9a** (165 mg, 0.50 mmol), and the mixture was stirred at room temperature for 7 h. The reaction was quenched with saturated aqueous potassium sodium tartrate solution at 0 °C. The resultant mixture was extracted with CH_2Cl_2 and the combined organic layer was washed with brine, dried, and concentrated. Purification of the residue by flash chromatography (silica gel, BW300, 30→50% EtOAc/hexane) gave **10a** (194 mg, quant.) as a colorless oil. The physicochemical properties are described in Table 7.

4.3.2. Method B. The following reaction was carried out under an atmosphere of argon. To a solution of **11a** (see below) (814 mg, 2.00 mmol) in anhydrous THF/toluene (20 mL, 1:1, v/v) were added benzylamine (0.660 mL, 6.04 mmol) and $AgOCOCF_3$ (486 mg, 2.20 mmol). After being stirred at 60 °C for 1.5 h, the reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 and 10% aqueous NH_4OH. The mixture was stirred vigorously at room temperature for ca. 10 min and then insoluble materials were filtered off. The organic layer was extracted with CH_2Cl_2, dried, and concentrated. Purification of the residue by flash chromatography (silica gel, BW300, 40% EtOAc/hexane) gave **10a** (780 mg, 100%). Similarly, 3-aryl-3,4-dihydro-4-oxo-2-quinazolinecarboxamides (**10b** and **10d**–**g**) were prepared from **9b** and **9c**–**g** by Method A. Compounds **10c**, **12a**–**c**, **13a**, **14a**, **15a**, **16b** and **17** were prepared from the corresponding 4-tolylthiol esters (**11a**–**c**)

Table 6. Physicochemical properties of 3-aryl-3,4-dihydro-4-oxo-quinazoline-2-carboxylic acid ethyl esters (**9a–g**)



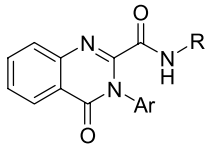
Compound	Ar	Yield (%)		Mp (°C)	NMR[b]	HRFABMS [(M+H)$^+$], calcd (found)
		Method[a] A	Method[a] B			
9a	2-Chloro-3-pyridyl	94	100	95–97	^{1}H NMR δ 8.54 (m, 1H), 8.36 (d, J=7.6 Hz, 1H), 7.94–7.85 (m, 2H), 7.79 (m, 1H), 7.64 (m, 1H), 7.45 (m, 1H), 4.25 (q, J=7.2 Hz, 2H), 1.18 (t, J=7.2 Hz, 3H); ^{13}C NMR δ160.3, 160.2, 150.3, 149.6, 146.1, 144.8, 139.1, 135.5, 131.7, 129.3, 128.7, 127.4, 123.1, 121.9, 63.3, 13.7	$C_{16}H_{13}ClN_3O_3$ 330.0645 (330.0650)
9b	–C_6H_4–*p*-CF_3	82	94	151–153	^{1}H NMR δ8.36 (d, J=8.4 Hz, 1H), 7.87 (d, J=3.6 Hz, 2H), 7.80 (d, J=8.0 Hz, 2H), 7.62 (m, 1H), 7.51 (d, J=8.0 Hz, 2H), 4.13 (q, J=7.2 Hz, 2H), 1.04 (t, J=7.2 Hz, 3H); ^{13}C NMR δ160.64, 160.60, 146.4, 146.2, 139.4, 135.3, 131.9, 131.6, 129.0, 128.8, 128.4, 127.3, 126.6 (q, J=4.0), 124.9, 122.2, 122.0, 63.0, 13.5	$C_{18}H_{14}F_3N_2O_3$ 363.0956 (363.0943)
9c	–C_6H_4–*o*-CO_2Me	72	87	67–68	^{1}H NMR δ8.34 (d, J=8.4 Hz, 1H), 8.27 (d, J=8.4 Hz, 1H), 7.90–7.80 (m, 3H), 7.70 (m, 1H), 7.63–7.55 (m, 2H), 7.40 (d, J=8.0 Hz, 1H), 4.10 (q, J=7.2 Hz, 2H), 3.71 (s, 3H), 1.04 (t, J=7.2 Hz, 3H); ^{13}C NMR δ164.6, 161.3, 160.6, 146.6, 146.3, 136.6, 134.9, 133.4, 131.9, 130.4, 129.9, 128.5, 128.33, 128.27, 127.3, 122.2, 62.7, 52.5, 13.5	$C_{19}H_{17}N_2O_5$ 353.1137 (353.1136)
9d	–C_6H_4–*p*-CN	60	89	173–175	^{1}H NMR δ8.34 (br, 1H), 7.87 (d, J=3.6 Hz, 2H), 7.83–7.79 (m, 2H), 7.63 (m, 1H), 7.50 (d, J=9.2 Hz, 2H), 4.16 (q, J=7.2 Hz, 2H), 1.11 (t, J=7.2 Hz, 3H); ^{13}C NMR δ 160.48, 160.46, 146.2, 145.6, 140.4, 135.4, 133.2, 129.19, 129.15, 128.5, 127.3, 121.9, 117.7, 113.6, 63.2, 13.6	$C_{18}H_{13}N_3O_3$ 320.1035 (320.1034)
9e	–C_6H_4–*m*-CF_3	77	98	112–113	^{1}H NMR δ8.35 (d, J=8.0 Hz, 1H), 7.87 (d, J=3.6 Hz, 2H), 7.78 (d, J=7.6 Hz, 1H), 7.71–7.56 (m, 4H), 4.13 (q, J=7.2 Hz, 2H), 1.05 (t, J=7.2 Hz, 3H)	$C_{19}H_{14}F_3NO_3$ 362.1004 (362.1002)
9f[26]	–C_6H_4–*p*-OMe	46	84	120–121 (lit.[26] 125–126)	^{1}H NMR δ8.35 (d, J=7.6 Hz, 1H), 7.83 (d, J=4.0 Hz, 2H), 7.59 (m, 1H), 7.33–7.26 (m, 2H), 7.04–6.96 (m, 2H), 4.13 (q, J=7.2 Hz, 2H), 3.86 (s, 3H), 1.07 (t, J=7.2 Hz, 3H); ^{13}C NMR δ161.2, 161.0, 160.3, 147.6, 146.6, 134.9, 129.4, 128.41, 128.38, 128.1, 127.3, 122.1, 114.6, 62.7, 55.6, 13.6	$C_{18}H_{17}N_2O_4$ 325.1188 (325.1172)
9g[26]	–Ph	51	98	105–106 (lit.[26] 108–109)	^{1}H NMR δ8.35 (d, J=8.0 Hz, 1H), 7.89–7.80 (m, 2H), 7.60 (m, 1H), 7.54–7.45 (m, 3H), 7.37 (m, 1H), 4.09 (q, J=7.2 Hz, 2H), 1.00 (t, J=7.2 Hz, 3H); ^{13}C NMR δ160.9, 147.2, 146.6, 136.1, 135.0, 129.6, 129.4, 128.5, 128.2, 127.3, 122.2, 62.7, 13.5	$C_{17}H_{15}N_2O_3$ 295.1082 (295.1071)

[a] See Section 4.2.2.
[b] ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were taken in $CDCl_3$.

and amines by Method B. The physicochemical properties are listed in Table 7.

4.3.3. 3,4-Dihydro-4-oxo-3-(2-chloro-3-pyridyl)-2-quinazolinecarbothioic acid S-*p*-tolyl ester (11a). The following reaction was carried out under an atmosphere of argon. To a solution of *p*-tolylthiol (497 mg, 4.00 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C was added dropwise a solution of $AlMe_3$ (1.0 M solution in hexane, 4.00 mL, 4.00 mmol). After being stirred at room temperature for 30 min, the mixture was cooled to 0 °C. To this solution was added quinazolin-4-one **9a** (329 mg, 1.00 mmol) and the mixture was stirred at room temperature for 80 min and then cooled to 0 °C. The reaction was carefully quenched with saturated aqueous potassium sodium tartrate. The resultant mixture was diluted with EtOAc and stirred at room temperature until the layers became clear. The organic layer was separated and washed with brine, dried, and concentrated. Purification of the residue by column chromatography (silica gel, BW300, 15→25% EtOAc/hexane) gave **11a** (356 mg, 87%). Crystallization from *i*-Pr_2O gave **11a** as pale yellow crystals: Mp 203–204 °C (*i*-Pr_2O); IR (film)

Table 7. Physicochemical properties of 3-aryl-3,4-dihydro-4-oxo-2-quinazolinecarboxyamides (**10a–g**, **12a–c**, **13a**, **14a**, **15a**, **16b**, **17**)



Compound	Ar	R	Method[a]	Yield (%)	Mp (°C)	NMR[b]	HRFABMS $[(M+H)^+]$ calcd (found)
10a	2-Chloro-3-pyridyl	$-CH_2Ph$	A B	100 100	Oil	^{1}H NMR δ 8.51 (m, 1H), 8.35 (d, J=9.2 Hz, 1H), 8.09 (br, 1H), 7.86 (m, 1H), 7.81–7.75 (m, 2H), 7.63 (m, 1H), 7.40–7.22 (m, 5H), 4.54 (m, 1H), 4.43 (m, 1H); ^{13}C NMR δ 161.1, 159.3, 149.3, 148.2, 145.3, 144.8, 138.4, 137.0, 135.3, 132.7, 129.0, 128.7, 128.0, 127.7, 127.6, 124.4, 122.9, 121.7, 43.6	$C_{12}H_{16}ClN_4O_2$ 391.0962 (391.0962)
10b	$-C_6H_4-p$-CF_3	$-CH_2Ph$	A	76	227–228	^{1}H NMR δ 8.33 (d, J=6.4 Hz, 1H), 7.90–7.81 (m, 2H), 7.80–7.72 (m, 3H), 7.62 (m, 1H), 7.43–7.30 (m, 6H), 4.46 (d, J=6.4 Hz, 2H)	$C_{23}H_{15}F_3N_3O_2$ 424.1273 (424.1281)
10c	$-C_6H_4-o$-CO_2Me	$-CH_2Ph$	B	91	Oil	^{1}H NMR δ 8.29 (d, J=7.3 Hz, 1H), 8.14 (m, 1H), 7.98 (t, J=5.5 Hz, 1H), 7.83–7.74 (m, 2H), 7.70 (m, 1H), 7.58–7.51 (m, 2H), 7.38 (d, J=7.3 Hz, 1H), 7.33–7.23 (m, 2H), 7.20–7.13 (m, 2H), 4.47 (dd, J=14.7, 5.5 Hz, 1H), 4.34 (dd, J=14.7 Hz, 5.5, 1H), 3.65 (s, 3H); ^{13}C NMR δ 165.3, 162.1, 160.0, 146.5, 145.8, 138.4, 134.7, 133.2, 131.4, 130.0, 128.9, 128.6, 128.3, 127.8, 127.6, 127.5, 12.3, 126.7, 122.1, 52.1, 43.4	$C_{24}H_{20}N_3O_4$ 414.1454 (414.1451)
10d	$-C_6H_4-p$-CN	$-CH_2Ph$	A	53	220–222	^{1}H NMR δ 8.32 (d, J=8.4 Hz, 1H), 7.97 (br s, 1H), 7.86 (m, 1H), 7.82–7.75 (m, 3H), 7.62 (t, J=8.0 Hz, 1H), 7.42–7.31 (m, 5H), 7.28–7.23 (m, 2H), 4.46 (d, J=6.4 Hz, 2H); ^{13}C NMR δ 163.2, 159.1, 145.0, 144.8, 136.7, 135.0, 132.6, 128.9, 128.5, 128.3, 127.7, 127.6, 127.5, 127.2, 121.5, 117.9, 112.5, 43.4	$C_{23}H_{16}N_4O_2$ 381.1351 (381.1358)
10e	$-C_6H_4-m$-CF_3	$-CH_2Ph$	A	93	174–175	^{1}H NMR δ 8.32 (d, J=8.4 Hz, 1H), 7.88–7.78 (m, 2H), 7.77–7.72 (m, 2H), 7.67–7.57 (m, 2H), 7.56–7.48 (m, 2H), 7.38–7.28 (m, 3H), 7.25 (m, 1H), 4.56–4.32 (m, 2H); ^{13}C NMR δ 162.0, 160.1, 146.4, 145.8, 138.3, 137.4, 135.5, 131.8, 129.8, 129.3, 129.1, 128.3, 128.12, 128.05, 127.8, 126.0 (q, J=4.0), 124.70, 124.66, 122.2, 44.0	$C_{23}H_{17}F_3N_3O_2$ 424.1272 (424.1264)
10f	$-C_6H_4$-p-OMe	$-CH_2Ph$	A	96	182–184	^{1}H NMR δ 8.32 (d, J=8.4 Hz, 1H), 7.80 (m, 1H), 7.73 (m, 1H), 7.60–7.53 (m, 2H), 7.37–7.28 (m, 2H), 7.25–7.18 (m, 3H), 7.03–6.97 (m, 2H), 4.46 (d, J=8.4 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR δ 161.6, 160.2, 159.3, 145.5, 136.9, 134.4, 128.34, 128.29, 128.0, 127.4, 127.3, 126.9, 126.7, 121.6, 113.9, 82.9, 55.1, 43.1	$C_{23}H_{20}N_3O_3$ 386.1504 (386.1505)
10g	–Ph	$-CH_2Ph$	A	78	154–155	^{1}H NMR δ 8.24 (d, J=8.4 Hz, 1H), 7.78–7.63 (m, 4H), 7.55–7.41 (m, 5H), 7.32–7.22 (m, 3H), 7.16 (d, J=6.4 Hz, 1H), 4.38 (d, J=8.4 Hz, 2H); ^{13}C NMR δ 161.6, 160.5, 147.8, 145.8, 137.3, 136.8, 134.7, 128.9, 128.6, 128.4, 127.73, 127.68, 127.6, 127.5, 127.1, 121.8, 43.4	$C_{22}H_{17}N_3O_2$ 356.1399 (356.1382)

Table 7 (*continued*)

Compound	Ar	R	Method[a]	Yield (%)	Mp (°C)	NMR[b]	HRFABMS $[(M+H)^+]$ calcd (found)
12a	2-Chloro-3-pyridyl	–Ph	B	100	213–214	^{1}H NMR δ 9.73 (s, 1H), 8.50 (m, 1H), 8.36 (d, J=8.2 Hz, 1H), 7.94–7.86 (m, 2H), 7.78 (m, 1H), 7.66 (m, 1H), 7.56 (d, J=7.3 Hz, 2H), 7.44 (m, 1H), 7.37–7.29 (m, 2H), 7.15 (m, 1H); ^{13}C NMR δ 161.1, 156.7, 149.3, 148.3, 145.0, 144.6, 138.2, 136.5, 135.5, 132.8, 129.3, 129.1, 128.1, 127.7, 125.2, 123.0	$C_{20}H_{14}ClN_4O_2$ 377.0805 (377.0803)
12b	–C_6H_4–*p*-CF_3	–Ph	B	81	199–200	^{1}H NMR δ 9.58 (s, 1H), 8.36 (d, J=8.2 Hz, 1H), 7.93–7.83 (m, 2H), 7.78 (d, J=8.2 Hz, 2H), 7.65 (m, 1H), 7.54 (d, J=8.2 Hz, 1H), 7.42 (d, J=8.2 Hz, 1H), 7.34 (t, J=8.2 Hz, 2H), 7.15 (m, 1H)	$C_{22}H_{15}F_3N_3O_2$ 410.1116 (410.1116)
12c	–C_6H_4–*o*-CO_2Me	–Ph	B	87	Amorphous	^{1}H NMR δ 9.73 (s, 1H), 8.32 (d, J=8.2 Hz, 1H), 8.16 (d, J=8.2 Hz, 1H), 7.84 (d, J=8.2 Hz, 2H), 7.70 (m, 1H), 7.62–7.47 (m, 4H), 7.38 (d, J=7.3 Hz, 1H), 7.27 (d, J=7.3 Hz, 2H), 7.09 (t, J=7.3 Hz, 1H), 3.68 (s, 3H); ^{13}C NMR δ 165.4, 162.2, 157.3, 146.0, 145.4, 138.6, 136.9, 134.8, 133.3, 131.5, 129.8, 128.93, 128.86, 128.6, 127.9, 127.4, 126.6, 124.8, 122.1, 119.9, 52.2	$C_{23}H_{18}N_3O_4$ 400.1297 (400.1317)
13a	2-Chloro-3-pyridyl	–C_6H_4–*p*-OMe	B	100	178–179	^{1}H NMR δ 9.66 (s, 1H), 8.47 (m, 1H), 8.39 (d, J=8.2 Hz, 1H), 7.92–7.80 (m, 2H), 7.76 (m, 1H), 7.61 (m, 1H), 7.49–7.37 (m, 3H), 6.88–6.77 (m, 2H), 3.75 (s, 3H); ^{13}C NMR δ 161.1, 156.9, 156.5, 149.1, 148.2, 145.0, 144.7, 138.1, 135.3, 132.8, 129.6, 129.1, 128.0, 127.4, 122.9, 121.6, 114.1, 55.3	$C_{21}H_{16}ClN_4O_3$ 407.0911 (407.0914)
14a	2-Chloro-3-pyridyl	–C_6H_4–*p*-CF_3	B	100	118–120	^{1}H NMR δ 9.98 (s, 1H), 8.49 (dd, J=4.5 Hz, 1.8, 1H), 8.34 (d, J=7.3 Hz, 1H), 7.92–7.83 (m, 2H), 7.78 (dd, J=7.3, 1.8 Hz, 1H), 7.68 (d, J=8.2 Hz, 2H), 7.64 (m, 1H), 7.56 (d, J=8.2 Hz, 2H), 7.43 (m, 1H); ^{13}C NMR δ 161.0, 156.9, 149.3, 148.3, 144.8, 144.0, 139.6, 138.2, 135.5, 132.6, 129.5, 128.1, 127.6, 126.6, 126.2 (q, J=4.0), 123.0, 122.5, 121.8, 119.7	$C_{21}H_{13}ClN_4O_2$ 445.0679 (445.0678)
15a	2-Chloro-3-pyridyl	–CH_2CH_2Ph	B	100	Oil	^{1}H NMR δ 8.49 (m, 1H), 8.32 (d, J=8.2 Hz, 1H), 7.90–7.79 (m, 2H), 7.77–7.70 (m, 2H), 7.61 (t, J=7.3 Hz, 1H), 7.42 (dd, J=7.3 Hz, 4.6, 1H), 7.35–7.28 (m, 2H), 7.27–7.17 (m, 2H), 3.63–3.46 (m, 2H), 2.85 (t, J=7.3 Hz, 2H); ^{13}C NMR δ 161.1, 159.3, 149.3, 148.3, 145.3, 144.8, 138.4, 138.3, 135.3, 132.8, 129.0, 128.7, 128.6, 128.0, 127.5, 126.6, 122.9, 121.8, 40.9, 35.4	$C_{22}H_{17}ClN_4O_2$ 405.1118 (405.1125)
16b	–C_6H_4–*p*-CF_3	*n*-Bu	B	96	198–199	^{1}H NMR δ 8.30 (d, J=7.3 Hz, 1H), 7.84 (m, 1H), 7.76 (t, J=8.2 Hz, 2H), 7.63–7.52 (m, 2H), 7.40 (d, J=8.2 Hz, 2H), 3.32–3.20 (m, 2H), 1.57–1.46 (m, 2H), 1.40–1.28 (m, 2H), 0.92 (t, J=7.3 Hz, 3H); ^{13}C NMR δ 161.7, 159.8, 146.1, 145.6, 140.8, 135.1, 130.9, 130.6, 128.9, 128.1, 127.9, 127.4, 126.1 (q, J=4.0 Hz), 125.1, 122.4, 121.9, 39.5, 31.3, 20.0, 13.6	$C_{20}H_{19}F_3N_3O_2$ 390.1429 (390.1428)
17	2-Chloro-3-pyridyl	–C_6H_3−3, 5-$(CF_3)_2$	B	100	Oil	^{1}H NMR δ 8.50–8.39 (m, 2H), 8.34 (d, J=8.2 Hz, 1H), 7.88 (m, 1H), 7.82–7.70 (m, 4H), 7.63 (m, 1H), 7.43 (m, 1H), 4.67–4.54 (m, 2H)	$C_{23}H_{14}ClF_6N_4O_2$ 527.0709 (527.0709)

[a] See Sections 4.3.1 and 4.3.2.
[b] ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were taken in $CDCl_3$.

3070, 2920, 1698, 1597, 1493, 1465, 1413, 1339, 1279, 1223, 1119, 1076, 1034, 1017, 882, 810, 791, 774 cm^{-1}; ^1H NMR δ 8.48–8.43 (m, 1H), 8.41 (d, J=6.4 Hz, 1H), 8.00 (d, J=8.2 Hz, 1H), 7.94 (m, 1H), 7.73–7.66 (m, 2H), 7.37 (m, 1H), 7.30–7.24 (m, 2H), 7.20 (d, J=8.2 Hz, 2H), 2.35 (s, 3H); HRFABMS calcd for $C_{21}H_{15}ClN_3O_2S$ [$(M+H)^+$] 408.0573, found 408.0583.

4.3.4. 3,4-Dihydro-4-oxo-3-[4-(trifluoromethyl)phenyl]-2-quinazolinecarbothioic acid S-*p*-tolyl ester (11b). Prepared according to the procedure described for **11a**. Yield 60% (colorless crystals): Mp 247 °C (*i*-Pr_2O); IR (film) 3074, 2924, 1690, 1670, 1595, 1495, 1470, 1417, 1329, 1279, 1161, 1122, 1070, 1045, 1021, 891, 848, 805, 776 cm^{-1}; ^1H NMR δ 8.36 (d, J=6.4 Hz, 1H), 8.00–7.88 (m, 2H), 7.73 (d, J=8.4 Hz, 2H), 7.66 (m, 1H), 7.42 (d, J=8.4 Hz, 2H), 7.24–7.15 (m, 4H), 2.35 (s, 3H); HRFABMS calcd for $C_{23}H_{16}F_3N_2O_2S$ [$(M+H)^+$] 441.0884, found 441.0884.

4.3.5. 3,4-Dihydro-4-oxo-3-[2-(methoxycarbonyl)-phenyl]-2-quinazolinecarbothioic acid S-*p*-tolyl ester (11c). Prepared according to the procedure described for **11a**. Yield 91% (a colorless oil); IR (film) 3028, 2952, 1720, 1694, 1594, 1566, 1491, 1465, 1346, 1271, 1188, 1102, 1082, 1049, 962, 883, 810, 758 cm^{-1}; ^1H NMR δ 8.34 (d, J=8.2 Hz, 1H), 8.13 (m, 1H), 7.97 (d, J=8.2 Hz, 1H), 7.88 (m, 1H), 7.68–7.58 (m, 2H), 7.52 (m, 1H), 7.31 (d, J=8.2 Hz, 1H), 7.23–7.13 (m, 4H), 3.71 (s, 3H), 2.32 (s, 3H); ^{13}C NMR δ 187.2, 161.8, 147.0, 145.9, 140.1, 137.1, 134.9, 134.5, 133.4, 131.8, 130.2, 130.0, 129.3, 129.1, 128.6, 127.4, 127.2, 123.5, 122.5, 52.3, 21.3; HRFABMS calcd for $C_{24}H_{19}N_2O_4S$ [$(M+H)^+$] 431.1065, found 431.1074.

4.4. *N*-[3,5-Bis(trifluoromethyl)benzyl]-3-(2-chloro-3-pyridyl)-3,4-dihydro-*N*-methyl-4-oxo-2-quinazolinecarboxamide (18)

Compound **18** was prepared from the 4-tolylthiol ester **11b** and *N*-3,5-bis(trifluoromethyl)benzyl-*N*-methylamine according to the procedure described in 4.3.2 (Method B). A pale yellow foam. Yield 100%. IR (film) 3074, 2936, 1699, 1655, 1604, 1568, 1471, 1414, 1382, 1351, 1281, 1175, 1133, 967, 908, 775 cm^{-1}; ^1H NMR (a 3:2 mixture of *cis–trans* isomers) δ 8.55 (m, 0.4H), 8.46 (m, 0.6H), 8.34 (m, 1H), 8.19 (s, 1H), 8.04–7.75 (m, 4H), 7.68–7.53 (m, 2H), 7.49 (m, 0.4H), 7.40 (m, 0.6H), 5.30 (d, J=15.6 Hz, 0.4H), 4.75 (d, J=15.6 Hz, 0.6H), 4.49 (d, J=15.6 Hz, 0.4H), 4.30 (d, J=15.6 Hz, 0.6H), 3.22 (s, 1.8H), 2.79 (s, 1.2H); HRFABMS calcd for $C_{24}H_{16}ClF_6N_4O_2$ [$(M+H)^+$] 541.0865, found 541.0880.

4.5. Intramolecular S_NAr reaction of 2-carboxamido-3-arylquinazolin-4-ones

4.5.1. 3,4-Dihydro-*N*-(substituted)-*N*-(substituted)aryl-4-oxo-2-quinazolinecarboxamides (19, 20, 22–25, 30–35). Typical examples are described for the formation of *N*-benzyl-3,4-dihydro-*N*-methyl-4-oxo-2-quinazolinecarboxamide (**19**) and *N*-benzyl-*N*-(2-chloro-3-pyridyl)-3,4-dihydro-4-oxo-2-quinazolinecarboxamide (**20**) by migration of **17a**. Formation of **19**: To a solution of **17a** (82 mg, 0.16 mmol) in DMF (2.5 mL) cooled at 0 °C was added NaH (60% in oil) (7.5 mg, 0.19 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 1 h. To this mixture cooled at 0 °C was added MeI (0.100 mL, 1.61 mmol). The mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous NH_4Cl at 0 °C and diluted with EtOAc. The organic layer was washed with water and brine, dried, and concentrated. Purification of the residue by flash chromatography (silica gel, BW300, 30% EtOAc/hexane) gave the migrated product **19** (69 mg, 81%). The physicochemical data are listed in Table 8.

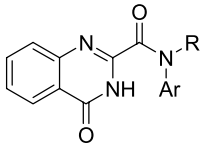
4.5.2. *N*-Benzyl-*N*-(2-chloro-3-pyridyl)-3,4-dihydro-4-oxo-2-quinazolinecarboxamide (20). To a solution of **10a** (900 mg, 2.31 mmol) in reagent grade DMF (20 mL) at 0 °C was added NaH (60% in oil) (110 mg, 2.75 mmol). After being stirred at room temperature for 1 h, the mixture was cooled to 0 °C and the reaction quenched with H_2O and solid NH_4Cl (150 mg). The resultant mixture was diluted with EtOAc, washed with H_2O and brine, dried, and concentrated. Purification of the residue by flash chromatography (silica gel, chromatorex–NH, 10% MeOH/$CHCl_3$) gave **20** (680 mg, 76%). Crystallization from EtOAc/hexane gave **20** as colorless crystals. The physicochemical properties are described in Table 8. Similarly, the migrated products **22–25** (Table 2) and **30–35** (Table 3) were obtained from the corresponding amides **12a–15a**, **10b**, **12b**, **16b**, **10c**, **12c** and **10d**. The physicochemical data are listed in Table 8.

4.6. Structural confirmation of the product of the intramolecular S_NAr reaction

4.6.1. 3-Methyl-3,4-dihydro-4-oxo-2-quinazolinecarboxylic acid ethyl ester (40).[17] The following reaction was carried out under an atmosphere of argon. To a solution of 3,4-dihydro-4-oxo-2-quinazolinecarboxylic acid ethyl ester **39**[11] (218 mg, 1.00 mmol) in DMF (10 mL) cooled at 0 °C were added MeI (0.310 mL, 4.98 mmol) and NaHMDS (1.20 mL, 1.20 mmol). After being stirred at room temperature for 100 min, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc and the organic layer was washed with water and brine, dried, and concentrated. Purification of the residue by flash chromatography (silica gel, chromatorex–NH, 20% EtOAc/hexane) gave **40**[17] (167 mg, 72%) as colorless crystals: Mp 41 °C (lit[17] 45 °C); IR (film) 2983, 1740, 1684, 1605, 1468, 1377, 1300, 1251, 1115, 1088, 1001, 863, 774 cm^{-1}; ^1H NMR δ 8.32 (d, J=7.6 Hz, 1H), 7.82–7.72 (m, 2H), 7.56 (m, 1H), 4.53 (q, J=7.3 Hz, 2H), 3.65 (s, 3H), 1.48 (t, J=7.3 Hz, 3H); ^{13}C NMR δ 161.39, 161.36, 147.1, 146.4, 134.5, 128.3, 128.0, 126.9, 121.8, 63.3, 32.1, 14.0; HRFABMS calcd for $C_{12}H_{13}N_2O_3$ [$(M+H)^+$] 233.0926, found 233.0921.

4.6.2. 3,4-Dihydro-4-oxo-3-methyl-2-quinazolinecarbothioic acid S-*p*-tolyl ester (41). The following reaction was carried out under an atmosphere of argon. To a solution of *p*-tolylthiol (1.44 g, 11.6 mmol) in anhydrous toluene (20 mL) cooled at 0 °C was added $AlMe_3$ (11.3 mL, 1.03 M solution in hexane, 11.6 mmol). The mixture was allowed to warm to room temperature over 30 min. To this solution was added **40** (673 mg, 2.90 mmol) in anhydrous

Table 8. Physicochemical properties of *N*-(substituted)-*N*-(substituted)ary-3,4-dihydro-4-oxo-2-quinazolinecarboxyamides (**19**, **20**, **22**–**25**, **30**–**35**)



Compound	Ar	R	Mp (°C)	NMR[a]	HRFABMS $[(M+H)^+]$ calcd (found)
20	2-Chloro-3-pyridyl	–Bn	168–169	^{1}H NMR δ 10.17 (br s, 1H), 8.39 (m, 1H), 8.25 (m, 1H), 7.60 (t, J=8.2 Hz, 1H), 7.48 (t, J=7.3 Hz, 1H), 7.36–7.22 (m, 5H), 7.17 (d, J=7.3 Hz, 2H), 6.95 (d, J=8.2 Hz, 1H), 5.72 (d, J=14.7 Hz, 1H), 4.43 (d, J=14.7 Hz, 1H)	$C_{21}H_{16}ClN_4O_2$ 391.0962 (391.0962)
22	2-Chloro-3-pyridyl	–Ph	180–181	^{1}H NMR δ 10.35 (br s, 1H), 8.39 (m, 1H), 8.28 (d, J=8.2 Hz, 1H), 7.75 (d, J=8.2 Hz, 1H), 7.65 (m, 1H), 7.55–7.28 (m, 7H), 7.09 (m, 1H); ^{13}C NMR δ 161.0, 160.8, 149.6, 148.1, 147.3, 146.6, 143.8, 141.1, 138.0, 134.6, 129.5, 128.9, 128.4, 127.9, 126.6, 126.3, 126.2, 123.3, 122.6	$C_{20}H_{14}ClN_4O_3$ 377.0805 (377.0822)
23	2-Chloro-3-pyridyl	–C_6H_4–*p*-OMe	198–200	^{1}H NMR δ 11.0 (br s, 1H), 8.38 (m, 1H), 8.23 (d, J=7.2 Hz, 1H), 7.76 (d, J=8.2 Hz, 1H), 7.65 (m, 1H), 7.51 (m, 1H), 7.40–7.27 (m, 3H), 7.09 (m, 1H), 7.02–6.75 (m, 2H), 3.81 (s, 3H); ^{13}C NMR δ 161.1, 160.8, 158.9, 149.3, 147.8, 146.5, 143.9, 138.7, 137.8, 134.6, 133.8, 128.8, 128.4, 127.5, 126.6, 123.2, 122.5, 114.7, 55.4	$C_{21}H_{16}ClN_4O_3$ 407.0911 (407.0927)
24	2-Chloro-3-pyridyl	–C_6H_4–*p*-CF_3	110–112	^{1}H NMR δ 10.63 (br, 1H), 8.43 (d, J=3.7 Hz, 1H), 8.29 (d, J=7.3 Hz, 1H), 7.78 (m, 1H), 7.72–7.59 (m, 3H), 7.55–7.43 (m, 3H), 7.37 (m, 1H), 7.10 (d, J=7.3 Hz, 1H); ^{13}C NMR δ 161.1, 160.0, 149.7, 148.7, 146.4, 143.5, 138.2, 134.7, 129.1, 128.4, 126.7, 126.5 (q, J=4.0), 124.9, 123.4, 122.6, 122.2	$C_{21}H_{12}ClF_3N_4O_2$ 445.0679 (445.0668)
25	2-Chloro-3-pyridyl	–CH_2CH_2Ph	Oil	^{1}H NMR δ 10.40 (br, 1H), 8.40 (m, 1H), 8.25 (m, 1H), 7.60 (m, 1H), 7.48 (m, 1H), 7.34–7.15 (m, 7H), 6.97 (d, J=8.2 Hz, 1H), 4.40 (m, 1H), 3.82 (m, 1H), 3.18 (m, 1H), 3.02 (m, 1H); ^{13}C NMR δ 160.8, 160.3, 149.7, 148.0, 146.6, 143.2, 138.2, 137.8, 134.5, 128.8, 128.75, 128.72, 128.6, 128.4, 126.7, 126.5, 122.8, 122.5, 53.3, 33.3	$C_{22}H_{17}ClN_4O_2$ 405.1118 (405.1113)
30	–C_6H_4–*p*-CF_3	–Bn	172–173	^{1}H NMR δ 10.70 (s, 1H), 8.26 (d, J=7.2 Hz, 1H), 7.70–7.45 (m, 4H), 7.36–7.13 (m, 8H), 5.15 (br s, 2H)	$C_{23}H_{17}F_3N_3O_2$ 424.1273 (424.1277)
31	–C_6H_4–*p*-CF_3	–Ph	169–171	^{1}H NMR δ 10.58 (s, 1H), 8.28 (d, J=7.2 Hz, 1H), 7.69–7.58 (m, 3H), 7.50 (t, J=7.2 Hz, 1H), 7.45–7.23 (m, 7H), 7.18 (d, J=8.0 Hz, 1H)	$C_{22}H_{15}F_3N_3O_2$ 410.1116 (410.1105)
32	–C_6H_4–*p*-CF_3	–*n*-Bu	123–124	^{1}H NMR δ 10.51 (br, 1H), 8.25 (br, 1H), 7.75–7.30 (m, 6H), 7.00 (br, 1H), 3.96 (br, 2H), 1.68 (br, 2H), 1.46–1.33 (m, 2H), 0.98–0.90 (br, 3H)	$C_{20}H_{19}F_3N_3O_2$ 390.1429 (390.1434)
33	–C_6H_4–*o*-CO_2Me	–Bn	Oil	^{1}H NMR δ 10.21 (s, 1H), 8.21 (d, J=8.2 Hz, 1H), 7.83 (d, J=7.3 Hz, 1H), 7.60–7.48 (m, 2H), 7.45–7.39 (m, 2H), 7.32–7.15 (m, 6H), 6.98 (d, J=8.2 Hz, 1H), 5.18 (d, J=14.7 Hz, 1H), 4.90 (d, J=14.7 Hz, 1H), 3.61 (s, 3H); ^{13}C NMR δ 165.9, 161.1, 160.8, 147.0, 144.7, 142.5, 135.5, 134.2, 132.8, 130.9, 130.4, 129.7, 128.4, 128.3, 128.1, 127.9, 127.8, 126.4, 122.4, 55.6, 52.3	$C_{24}H_{20}N_3O_4$ 414.1454 (414.1457)
34[b]	–C_6H_4–*o*-CO_2Me	–Ph	Oil	^{1}H NMR δ 10.06 (br s, 1H), 8.23 (d, J=7.0 Hz, 1H), 8.10 (s, 0.26H), 7.90 (s, 0.74H), 7.75–7.05 (m, 11H), 3.90 (s, 0.78H), 3.78 (s, 2.21H)	$C_{23}H_{18}N_3O_4$ 400.1297 (400.1293)
35	–C_6H_4–*p*-CN	–Bn	149–151	^{1}H NMR δ 10.06 (br s, 1H), 8.26 (d, J=8.0 Hz, 1H), 7.69–7.57 (m, 3H), 7.49 (m, 1H), 7.35–6.95 (m, 8H), 5.18 (br s, 2H)	$C_{23}H_{17}N_4O_2$ 381.1351 (381.1339)

[a] ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were taken in $CDCl_3$.
[b] Exists as a 74:26 mixture of *cis*–*trans* isomers at 300 K.

toluene (15 mL) via cannula. After being stirred at room temperature for 1.5 h, the reaction mixture was cooled to 0 °C and treated with saturated aqueous potassium sodium tartrate solution and then with EtOAc. The mixture was stirred at room temperature until the layers became clear. The organic layer was separated, washed with brine, dried, and concentrated. Purification of the residue by flash chromatography (silica gel, BW300, 20% EtOAc/hexane) gave *p*-tolylthiol ester **41**, which was further purified by crystallization from *i*-Pr_2O to give pale yellow crystals

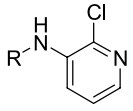
(642 mg, 71%): Mp 120–122 °C; IR (film) 3024, 2921, 1685, 1593, 1564, 1465, 1334, 1297, 1188, 1103, 1011, 918, 882, 809, 773 cm^{-1}; ^1H NMR δ 8.34 (d, J=7.2 Hz, 1H), 7.90–7.79 (m, 2H), 7.61 (m, 1H), 7.46–7.38 (m, 2H), 7.34–7.27 (m, 2H), 3.76 (s, 3H), 2.42 (s, 3H); HRFABMS calcd for $C_{17}H_{15}N_2O_2S$ [$(M+H)^+$] 311.0854, found 311.0843.

4.6.3. *N*-Benzyl-3,4-dihydro-3-methyl-*N*-[4-(trifluoromethyl)phenyl]-4-oxo-2-quinazolinecarboxamide (42). The following reactions were carried out under an atmosphere of argon. To a solution of **41** (150 mg, 0.48 mmol) in anhydrous THF/toluene (1:1, v/v, 6 mL) were added 4-aminobenzotrifluoride (0.180 mL, 1.43 mmol) and $AgOCOCF_3$ (118 mg, 0.53 mmol). The mixture was heated at 60 °C for 2.5 h. After cooling, the mixture was diluted with CH_2Cl_2 and 10% NH_4OH and stirred vigorously at room temperature for a while. Insoluble materials were filtered off, and the filtrate was extracted with CH_2Cl_2. The combined organic layer was dried, and concentrated. The residue was passed through a short plug of silica gel (BW300, 20% EtOAc/hexane) and used in the next reaction without further purification.

To a solution of the above material in DMF (5 mL) cooled at 0 °C were added benzyl bromide (0.070 mL, 0.59 mmol) and NaH (60% in oil) (19 mg, 0.48 mmol). After being stirred at room temperature for 80 min, the mixture was cooled to 0 °C and quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with water and brine, dried, and concentrated. Purification of the residue by flash chromatography (silica gel, BW300, 30% EtOAc/hexane) gave **42** as a colorless foam: IR (film) 3068, 3036, 1682, 1601, 1519, 1468, 1438, 1401, 1326, 1265, 1169, 1128, 1069, 1012, 967, 849, 776 cm^{-1}; ^1H NMR (exists as a 83:17 mixture of *cis–trans* isomers at 300 K) δ 8.31 (d, J=7.3 Hz, 0.17H), 8.16 (d, J=7.3 Hz, 0.83H), 7.83–7.08 (m, 12H), 5.14 (s, 0.34H), 5.05 (s, 1.66H), 3.61 (s, 0.51H), 3.38 (s, 2.49H); HRFABMS calcd for $C_{24}H_{19}F_3N_3O_2$ [$(M+H)^+$] 438.1429, found 438.1425.

4.6.4. *N*-Methylation of 30. To a solution of **30** (125 mg, 0.30 mmol) in DMF (4 mL) cooled at 0 °C were added MeI (0.180 mL, 2.89 mmol) and NaH (60% in oil) (14 mg, 0.35 mmol). After being stirred at room temperature for 50 min, the mixture was cooled to 0 °C and quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with water and brine, dried, and concentrated. Purification of the residue by flash chromatography

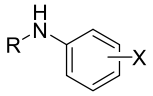
Table 9. Physicochemical properties of *N*-(2-chloro-3-pyridinyl)-*N*-(substituted)amines (**21**, **26**–**29**, **47**–**49**)



Compound	R	Mp (°C)	NMR[a]	HRFABMS [$(M+H)^+$] calcd (found)
21[27]	–CH_2Ph	Oil	^1H NMR δ 7.71 (d, J=4.4 Hz, 1H), 7.40–7.23 (m, 5H), 7.02 (m, 1H), 6.83 (d, J=8.4 Hz, 1H), 4.84 (br s, 1H), 4.39 (d, J=5.6 Hz, 2H); ^{13}C NMR δ 140.6, 137.7, 137.1, 136.7, 128.9, 127.6, 127.1, 123.4, 117.8, 47.4	$C_{12}H_{11}ClN_2$ 219.0689 (219.0688)
26	–Ph	69–71	^1H NMR δ 7.86 (d, J=4.8 Hz, 1H), 7.49 (d, J=8.0 Hz, 1H), 7.40–7.32 (m, 2H), 7.20–7.04 (m, 4H), 6.14 (s, 1H); ^{13}C NMR δ 140.0, 139.3, 138.6, 137.7, 129.7, 123.9, 123.1, 121.20, 121.15	$C_{11}H_{10}ClN_2$ 205.0532 (205.0538)
27	–C_6H_4–*p*-OMe	Oil	^1H NMR δ 7.78 (d, J=4.6 Hz, 1H), 7.18 (d, J=7.3 Hz, 1H), 7.12 (d, J=8.2 Hz, 2H), 7.02 (dd, J=8.2, 4.6 Hz, 1H), 6.92 (d, J=9.2 Hz, 2H), 5.99 (s, 1H), 3.82 (s, 3H); ^{13}C NMR δ 157.0, 139.3, 138.1, 137.4, 132.5, 125.2, 123.1, 119.8, 114.9, 55.5	$C_{12}H_{12}ClN_2O$ 235.0638 (235.0642)
28	–C_6H_4–*p*-CF_3	Oil	^1H NMR δ 7.99 (d, J=4.6 Hz, 1H), 7.64 (d, J=8.2 Hz, 1H), 7.58 (d, J=9.1 Hz, 2H), 7.23–7.13 (m, 3H), 6.29 (s, 1H); ^{13}C NMR δ 144.1, 141.5, 136.1, 127.3 (q, J=4.0), 125.1, 123.9, 123.4, 118.8	$C_{12}H_9ClF_3N_2$ 273.0406 (273.0401)
29	–CH_2CH_2Ph	Oil	^1H NMR δ 7.70 (dd, J=4.6, 1.8 Hz, 1H), 7.38–7.30 (m, 2H), 7.29–7.19 (m, 4H), 7.08 (dd, J=8.2, 4.6 Hz, 1H), 6.90 (m, 1H), 4.42 (s, 1H), 3.47–3.37 (m, 2H), 3.00–2.92 (m, 2H); ^{13}C NMR δ 140.5, 138.5, 137.1, 136.3, 128.73, 128.66, 126.7, 123.3, 117.3, 44.4, 35.2	$C_{13}H_{13}ClN_2$ 233.0845 (233.0842)
47	–C_6H_4–*o*-Me	Oil	^1H NMR δ 7.82 (dd, J=3.6, 1.6 Hz, 1H), 7.31 (m, 1H), 7.22 (d, J=3.6 Hz, 2H), 7.13 (m, 1H), 7.08–7.01 (m, 2H), 5.92 (s, 1H), 2.25 (s, 3H); ^{13}C NMR δ 138.5, 138.1, 138.0, 132.4, 131.4, 127.1, 125.2, 123.4, 123.1, 120.6, 17.8	$C_{12}H_{12}ClN_2$ 219.0689 (219.0687)
48[28]	–C_6H_4–*p*-Me	Oil	^1H NMR δ 7.83 (m, 1H), 7.37 (d, J=8.0 Hz, 1H), 7.17 (d, J=8.4 Hz, 2H), 7.09–7.01 (m, 3H), 6.07 (s, 1H), 2.34 (s, 3H); ^{13}C NMR δ 138.7, 138.4, 138.1, 137.2, 133.9, 130.2, 123.1, 122.1, 120.5, 20.9	$C_{12}H_{12}ClN_2$ 219.0689 (219.0695)
49	–*n*-Bu	Oil	^1H NMR δ 7.69 (m, 1H), 7.09 (m, 1H), 6.88 (m, 1H), 3.19–3.10 (m, 2H), 1.71–1.61 (m, 2H), 1.52–1.40 (m, 2H), 0.98 (t, J=7.2 Hz, 3H); ^{13}C NMR δ 140.9, 136.9, 136.0, 123.4, 117.2, 42.9, 31.1, 20.2, 13.8	$C_9H_{14}ClN_2$ 185.0845 (185.0842)

[a] ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were taken in $CDCl_3$.

Table 10. Physicochemical properties of *N*-(substituted)anilines (**50–54**)



Compound	X	R	Mp (°C)	NMR[a]	HRFABMS [(M+H)$^+$] calcd (found)
50	*p*-CF_3	–Ph	49–51	^{1}H NMR δ 7.46 (d, J=8.0 Hz, 2H), 7.37–7.28 (m, 2H), 7.14 (d, J=7.2 Hz, 2H), 7.08–6.99 (m, 3H), 5.90 (s, 1H); ^{13}C NMR δ 146.8, 141.1, 129.6, 126.7 (q, J=4.0 Hz), 122.9, 120.0, 115.3	$C_{13}H_{11}F_3N$ 238.0843 (238.0851)
51[29]	*p*-CF_3	–Bn	Oil	^{1}H NMR δ 7.42–7.26 (m, 7H), 6.63 (d, J=8.4 Hz, 2H), 4.37 (s, 1H); ^{13}C NMR δ 150.4, 138.4, 128.8, 127.5, 127.4, 126.6 (q, J=4.0), 126.3, 112.0, 47.8, 29.7	$C_{14}H_{13}F_3N$ 252.1000 (252.1008)
52	*p*-CF_3	–*n*-Bu	Oil	^{1}H NMR δ 7.38 (d, J=8.4 Hz, 2H), 6.58 (d, J=9.2 Hz, 2H), 3.93 (br s, 1H), 3.18–3.08 (m, 2H), 1.67–1.52 (m, 2H), 1.49–1.36 (m, 2H), 1.00–0.92 (m, 3H); ^{13}C NMR δ 150.9, 126.6 (q, J=4.0), 123.7, 118.2, 111.6, 43.2, 31.4, 20.2, 13.8	$C_{11}H_{15}F_3N$ 218.1156 (218.1162)
53[30]	*p*-CN	–Bn	61–63 (lit.[30] 66)	^{1}H NMR δ 7.45–7.28 (m, 7H), 6.60 (d, J=9.2 Hz, 2H), 4.73 (br s, 1H), 4.38 (d, J=5.6 Hz, 2H); ^{13}C NMR δ 151.0, 137.7, 133.8, 128.89, 128.88, 127.7, 127.4, 120.3, 112.5, 47.6	$C_{14}H_{13}N_2$ 209.1079 (209.1078)
54[31]	*p*-CN	–CH_2CH_2Ph	Oil	^{1}H NMR δ 7.44–7.13 (m, 7H), 6.58–6.48 (m, 2H), 4.21 (s, 1H), 3.48–3.38 (m, 2H), 2.95–2.85 (m, 2H); ^{13}C NMR δ 151.0, 138.4, 133.7, 128.8, 128.7, 120.4, 112.3, 100.0, 98.8, 44.2	$C_{15}H_{14}N_2$ 223.1235 (223.1236)

[a] ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were taken in $CDCl_3$.

(silica gel, BW300, 30% EtOAc/hexane) gave amide **42** (118 mg, 92%) as a colorless foam. Spectroscopic data of this material were indistinguishable with those of the authentic sample obtained from **41** (Scheme 3).

4.7. Synthesis of secondary aryl amines (21, 26–35) from the amides (Tables 1 and 2)

As a typical example, the synthesis of *N*-benzyl-*N*-(2-chloro-3-pyridinyl)amine (**21**) from the amide **10a** is described. To a solution of **10a** (100 mg, 0.26 mmol) in reagent grade DMF (5 mL) at 0 °C was added NaH (60% in oil) (51 mg, 1.28 mmol). After being stirred at room temperature overnight, the mixture was cooled to 0 °C and quenched with H_2O. The mixture was diluted and extracted with EtOAc, washed with H_2O and brine, dried, and concentrated. Purification of the residue by flash chromatography (silica gel, BW300, 10→20% EtOAc/hexane) gave **21**[27] (42 mg, 76%) as a colorless oil. Similarly, the secondary aryl amines (**26–35**) were obtained from the corresponding amides. The physicochemical properties are described in Tables 9 and 10.

4.8. Direct synthesis of secondary aryl amines (21, 26, 27 and 47–54) from 3-aryl-3,4-dihydro-4-oxo-2-quinazolinecarboxylic acid ethyl esters (9a, 9b and 9d) and amines (Table 4)

As a typical example, the preparation of *N*-(2-chloro-3-pyridinyl)-*N*-phenylamine (**26**) by reaction of **9a** with aniline in the presence of NaOMe is described. To a mixture of aniline (21 mg, 0.23 mmol) and NaOMe (41 mg, 0.76 mmol) in reagent grade THF (1 mL) at 0 °C was added **9a** (50 mg, 0.15 mmol). After being stirred at room temperature for 5 h, the mixture was diluted with EtOAc and acidified with AcOH (pH ~4). The mixture was diluted with EtOAc, washed with H_2O and brine, dried, and concentrated. Purification of the residue by flash chromatography (silica gel, BW300, 20% EtOAc/hexane) gave **26** (24 mg, 78%). The physicochemical properties are described in Table 9. Similarly, the secondary aryl amines **21**, **27** and **47–54** were obtained by reaction of **9a**, **9b** and **9d** with the various amines. The results are summarized in Table 4, and the physicochemical properties are listed in Tables 9 and 10.

Acknowledgements

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A new one-pot synthesis of α-Gal epitope derivatives involved in the hyperacute rejection response in xenotransplantation

Yuhang Wang, Qingyan Yan, Jingping Wu, Li-He Zhang and Xin-Shan Ye*

The State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Xue Yuan Rd #38, Beijing 100083, China

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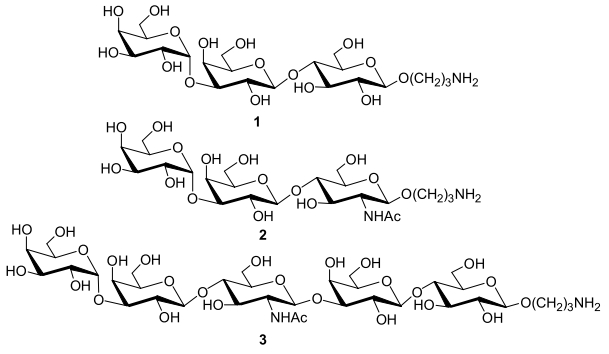
Abstract—Xenotransplantations from pig to human are rapidly rejected because of the interaction between α-Gal epitopes carried by the graft and natural antibodies (anti-Gal antibodies) present in the blood of the recipient. This paper describes a three-component one-pot synthesis of three α-Gal related oligosaccharides with minimal protecting group manipulations in a very short period of time.

1. Introduction

Nowadays the major barrier to a successful pig-to-human xenotransplantation is antibody- and complement-dependent hyperacute rejection (HAR),[1] known to be due to the specific interaction of recipient xenoreactive antibodies with antigens present on the endothelium of the donor organ, followed by activation of the complement cascade.[2] It has been identified that trisaccharides Galα1-3Galβ1-4Glcβ-R and Galα1-3Galβ1-4GlcNAcβ-R and pentasaccharide Galα1-3Galβ1-4GlcNAcβ1-3Galβ1-4Glcβ-R are the main α-Gal epitopes, which show high affinity with xenoreactive natural antibodies (XNAs) in human sera.[3] In order to prevent the hyperacute rejection, elimination or reduction of the interaction between α-Gal and anti-Gal have been studied by various approaches including anti-Gal immunoadsorption and anti-Gal neutralization.[4] Furthermore, α-Gal epitopes could be covalently attached to certain antiviral agents through appropriate linkers. The α-Gal-conjugated antiviral agents are envisaged to bind virus with α-Gal epitopes, resulting in the killing of the virus via antibody-mediated cytotoxicity and/or antibody-dependent, complement-mediated lysis of virus particles and virus-infected cells.[5] Such approaches would require access to a substantial amount of α-Gal oligosaccharides and α-Gal analogues.

Several methods were reported for the synthesis of α-Gal epitope oligosacchrides. Wang et al. described a chemoenzymatic approach to synthesize various α-Gal derivatives including trisaccharide and pentasaccharide epitopes based on the use of recombinant α(1–3)-galactosyltransferase.[6] Boons et al. reported a highly convergent synthesis of the methyl glycoside of the pentasaccharide.[7] And a direct synthesis of ceramide pentasaccharide based on the trichloroacetimidate methodology was carried out by the Schmidt group.[8] In the synthetic process of these oligosaccharides, the necessary regio- and stereocontrol often led to laborious synthetic transformations, tremendous protecting group manipulations, and tedious intermediate isolations which complicated the overall synthetic process and decreased synthetic efficiency. Herein we present a new method for the synthesis of two trisaccharides **1** and **2**, and a pentasaccharide **3** (Scheme 1) using a three-component one-pot strategy.[9] The aminopropyl group was incorporated as a side chain for further derivation.[10] We envisaged that the incorporation of the one-pot strategy with no intermediate work-up or purification may simplify this



Scheme 1. The structures of α-Gal oligosaccharide derivatives **1**, **2**, **3**.

Keywords: α-Galactosyl epitopes; One-pot synthesis; Glycosylations; Oligosaccharides; Xenotransplantation.
* Corresponding author. Tel.: +86 108 2801570; fax: +86 10 62014949; e-mail: xinshan@bjmu.edu.cn

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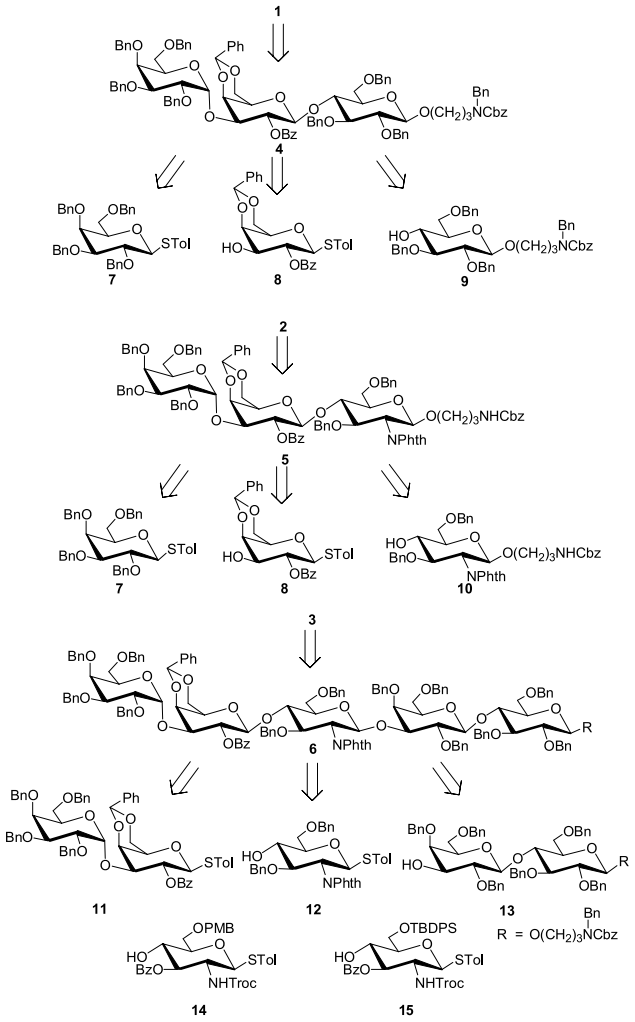
complicated synthetic operation and improve the synthetic efficiency.

2. Results and discussion

The initial design of building blocks and selection of protecting groups were the key step in our one-pot synthesis. The retrosynthetic analysis of α-Gal derivatives **1**, **2**, **3** is shown in Scheme 2. Fully protected trisaccharides **4** and **5** could both be divided into three units: a non-reducing end galactosyl, a hydroxy bridging galactosyl, and a side chain binding glucosyl or glucosaminyl unit. The fully protected pentasaccharide **6** was retrosynthetically disconnected into three saccharide building blocks: disaccharide building block **11**, glucosaminyl building block **12**, and lactosyl building block **13**. Implementation of one-pot oligosaccharide synthesis requires a descending order of reactivity for the three building blocks in each one-pot reaction. The non-reducing end unit should have the highest reactivity among the three components, and the reducing end component should have no reactivity due to its *O*-glycoside which cannot be activated by thioglycoside promoters. The selection of protecting groups was the main concern in the design of the in-between building blocks, because the presence of a free hydroxyl group and thiotoluene functionality would make it act as both a glycosyl acceptor and donor. Besides, their relative reactivities towards glycosylation should fall between non-reducing and reducing end component. To charge these building blocks with different reactivities, different protecting groups were used according to the reactivity order of thioglycosides based on the method which Wong group developed.[9a,c] Thus four functional building blocks **7**, **8**, **9**, and **10** were designed and synthesized for one-pot glycosylation of the two trisaccharides **4** and **5**. As for the one-pot synthesis of pentasaccharide **6**, building blocks **11** and **13** were used as non-reducing and reducing end unit, respectively. We designed three building blocks **12**, **14** and **15** for the choice of the in-between component of **6**, and it was demonstrated that only **12** was suitable for the one-pot synthesis by experiments.

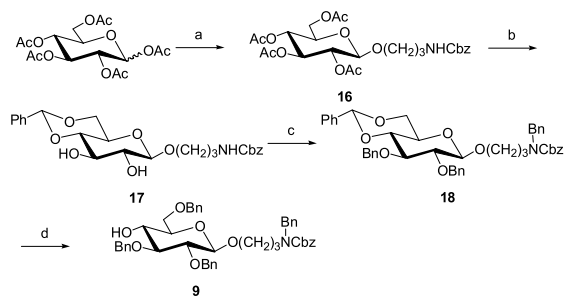


Scheme 2. The retrosynthetic analysis of one-pot synthesis of α-Gal derivative **1**, **2**, **3**.

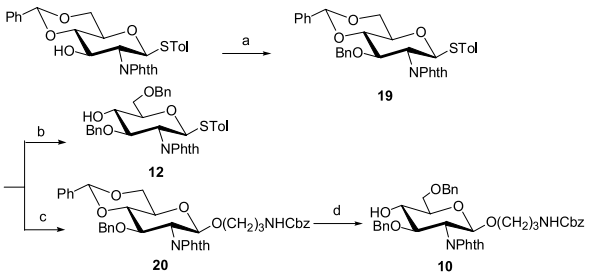
We chose thioglycosides as glycosyl donors due to the advantage that they are stable enough in most conditions and can be activated by a variety of promoters. In order to perform an efficient one-pot synthesis, we have tested several promoter systems, such as dimethyl(thiomethyl)sulfonium triflate (DMTST),[11] *N*-iodosuccinimide and triflic acid (NIS/TfOH),[12] phenylsulfenyl chloride and silver triflate (PhSCl/AgOTf),[13] 1-benzenesulfinyl piperidine and triflic anhydride (BSP/Tf_2O).[14] Eventually we found that NIS/TfOH was a suitable promoter for trisaccharide synthesis and BSP/Tf_2O was an efficient coupling agent for pentasaccharide synthesis.

2.1. Synthesis of building blocks

Building blocks **7** and **8** were prepared by literature procedures.[9a] The synthesis of glucosyl acceptor **9** was performed as depicted in Scheme 3. The synthesis was started from glucose pentaacetate, which was converted to the β-glucoside **16** by the reaction with benzyl *N*-(3-hydroxypropyl)-carbamate in the presence of $BF_3 \cdot Et_2O$. Deacetylation of **16** followed by 4,6-*O*-benzylidene protection produced saccharide **17**. The benzylation of the two remaining hydroxyls of **17** was performed using sodium hydride and benzyl bromide in DMF to give compound **18**. Subsequent selectively reductive cleavage of 4,6-*O*-benzylidene acetal of **18** gave the 4-OH exposed saccharide **9** in 88% yield.



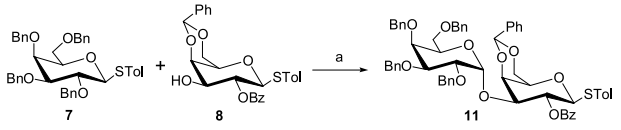
Scheme 3. (a) $HO(CH_2)_3NHCbz$, $BF_3 \cdot Et_2O$, CH_2Cl_2, rt, 41%; (b) (i) NaOMe/MeOH, rt; (ii) $PhCH(OMe)_2$, CSA, CH_3CN, rt, 66%; (c) BnBr/NaH/DMF, 0 °C to rt, 97%; (d) $HCl \cdot Et_2O/NaCNBH_3$/THF, rt, 88%.



Scheme 4. (a) BnBr/NaH/DMF, 0 °C to rt, 92%; (b) $HCl\cdot Et_2O/NaCNBH_3$/THF, rt, 90%. (c) $HO(CH_2)_3NHCbz/NIS/TfOH$, CH_2Cl_2, 4 Å MS, 0 °C, 49%; (d) $HCl\cdot Et_2O/NaCNBH_3$/THF, rt, 91%.

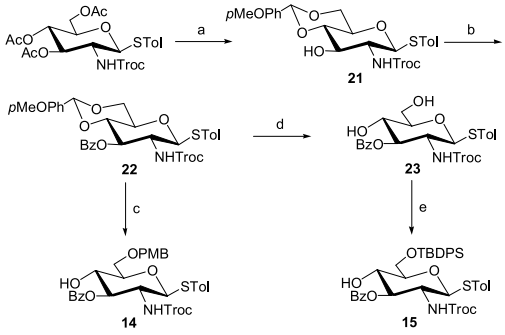
The synthesis of building blocks **10** and **12** was shown in Scheme 4. Benzylation of *p*-methylphenyl 4,6-*O*-benzylidene-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside[9a] gave saccharide **19** in 92% yield. Regioselective reductive ring-opening of 4,6-*O*-benzylidene acetal of **19** produced **12** in 90% isolated yield with the 4-hydroxyl group exposed.[15] And the coupling reaction between compound **19** and benzyl *N*-(3-hydroxypropyl)-carbamate was promoted by NIS/TfOH, producing compound **20**, followed by the same regioselective ring-opening reaction to give building block **10** (91% yield).

Building block **11** was synthesized by glycosylation between perbenzylated galactosyl thioglycoside donor **7** and galactosyl acceptor **8** (Scheme 5). We chose the donor and acceptor according to their relative reactivity values (RRV) measured by the Wong group.[9c] The large disparity of the reactivity between **7** and **8** (RRV of $\mathbf{7}=5.2\times10^4$, RRV of $\mathbf{8}=1791$) enables the high sequence selectivity of glycosidic coupling reaction. Much attention was paid to the choice of the glycosylation conditions. At first, we used DMTST[11] and NIS/TfOH[12] as promoters, respectively. However, the use of DMTST required a harsh condition. The operation inconvenience limited its use in this glycosylation reaction. In the presence of NIS/TfOH (1.1 or 1.2 equiv), donor **7** was coupled with acceptor **8** to give the target disaccharide **11** in moderate yield (54%), attributed to the formation of byproducts. Two possible byproducts could have formed. One is the succinimide product,[9a] the other is the hydrolyzed product due to the fact that the anomeric thiotoluene functionality of compound **11** could be further activated by the excessive NIS/TfOH and substituted by hydroxyl group after work-up with water. Finally, we turned our attention to BSP/Tf_2O,[14b] developed by Crich and Smith,[14a] in order to improve the efficiency of the glycosylation protocol. Utilizing BSP/Tf_2O as the promoter system, the coupling reaction of **7** and **8** proceeded smoothly, and the desired product was isolated in 90% yield.



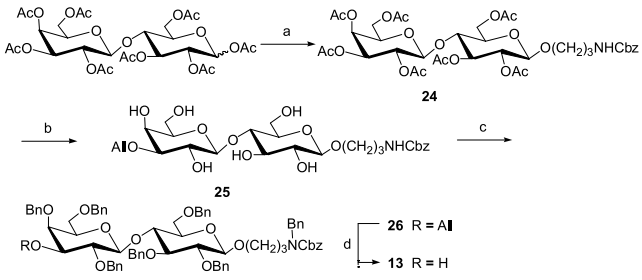
Scheme 5. (a) BSP, Tf_2O, CH_2Cl_2, 4 Å MS, −70 °C to rt, 90% or NIS, TfOH, CH_2Cl_2, 4 Å MS, 0 °C, 54%.

The preparation of building block **14** and **15** is summarized in Scheme 6. The synthesis was started from *p*-methylphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxylcarbonylamino)-1-thio-β-D-glucopyranoside,[9a] which was deacetylated by using NaOMe/MeOH, followed by the *p*-methoxylbenzylidene formation between C_4/C_6 hydroxyls to produce compound **21**. The remaining C_3 hydroxyl of **21** was converted to a benzoyl ester, giving fully protected thioglycoside **22**. Subsequent selective cleavage of 4,6-*O*-methoxylbenzylidene acetal of **22** gave 6-*O*-methoxylbenzyl ether **14** in 80% yield. Compound **23** was produced by removal of the *p*-methoxylbenzylidene protecting group, followed by the selective protection of C_6 hydroxyl by *tert*-butyldiphenylsilyl (TBDPS) group, yielding building block **15** in 86% yield.



Scheme 6. (a) (i) NaOMe/MeOH, rt; (ii) *p*-$CH_3OPhCH(OMe)_2$, CSA, CH_3CN, rt, 90%; (b) BzCl, pyridine, 0 °C, 83%; (c) $CF_3COOH/NaCNBH_3$/DMF, 4 Å MS, rt to 40 °C, 80%; (d) HOAc, rt, 91%; (e) TBDPSCl, imidazole, DMF, rt, 86%.

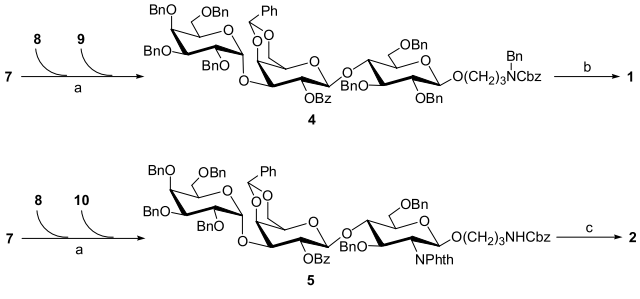
The synthesis of building block **13** began with lactose peracetate, which was converted to the β-lactoside **24** by reaction with benzyl *N*-(3-hydroxypropyl)-carbamate in the presence of $BF_3\cdot Et_2O$. Compound **24** was deacetylated by using NaOMe/MeOH, then treated with dibutyltin oxide, followed by the reaction with allyl bromide to provide selective 3′-*O*-allyl protected lactoside **25**. The following benzylation of the remaining hydroxyls of **25** was performed using sodium hydride and benzyl bromide in DMF to give compound **26**. And building block **13** was prepared by removal of the allyl protecting group of **26** using palladium (II) chloride (Scheme 7).[15]



Scheme 7. (a) $HO(CH_2)_3NHCbz$, $BF_3\cdot Et_2O$, CH_2Cl_2, rt, 43%; (b) (i) NaOMe/MeOH, rt; (ii) MeOH/Bu_2SnO, 110 °C; then $CH_2{=}CH{-}CH_2{-}Br$, Bu_4NI, C_6H_6, 120 °C, 4 Å MS; (c) BnBr/NaH/DMF, 0 °C, 70% from **24** to **26**; (d) $PdCl_2$, MeOH, rt, 98%.

2.2. The one-pot synthesis of fully protected α-Gal derivatives 4, 5, 6 and the preparation of their deprotected products 1, 2, 3

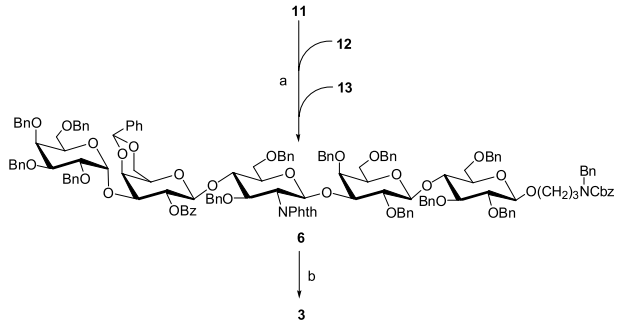
With all building blocks in hand, we began to assemble the three target oligosaccharides using a two-step three-component one-pot coupling protocol. The synthesis of the two trisaccharides was depicted in Scheme 8. The more reactive building block **7** was first activated in the presence of NIS/TfOH at 0 °C to couple with the less reactive building block **8** and the reaction was monitored by TLC. After complete consumption of donor **7** the third building block **9** along with another molar equivalent of NIS was then added. The resulting trisaccharide **4** was obtained in 55% isolated yield. The synthesis of **5** was identical with that of **4** except that the final acceptor used was building block **10**. Trisaccharide **5** was obtained also in 55% isolated yield. The yield of the two trisaccharides is higher than that of the disaccharide **11** (54%). This is presumably because that the *O*-functionality in the reducing end of the trisaccharides is innate to the thioglycoside promoters, which cannot undergo the byproduct formation process as disaccharide **11** (vide supra). Complete deprotection of **4** was involved in two steps: the benzoyl group was removed by NaOMe/MeOH, and the benzyl, benzylidene, and benzyl carbamate protecting groups were cleaved by catalytic hydrogenolysis over 10% Pd–C to give trisaccharide **1** (in the form of acetate) in 70% isolated yield. Full deprotection of **5** was accomplished as follows:[7] the phthalimido group was converted into an NHAc moiety by treatment with $NH_2NH_2 \cdot H_2O$ followed by reacetylation with acetic anhydride in pyridine, the benzoyl group was removed by NaOMe/MeOH, the benzyl, benzylidene and benzyl carbamate protecting groups were removed with Pd–C catalyzed hydrogenolysis to afford trisaccharide **2** (in the form of acetate) in 70% isolated yield. The α, β anomeric configurations of the two trisaccharides were conformed by their ^1H and ^{13}C NMR spectra referred to the structure of the pentasaccharide we reported recently.[15]



Scheme 8. (a) NIS, TfOH, CH_2Cl_2, 4 Å MS, 0 °C, 55% for **4**, 55% for **5**; (b) (i) NaOMe, MeOH; (ii) H_2, Pd–C, HOAc/THF/H_2O, 70%; (c) (i) $NH_2NH_2 \cdot H_2O$, EtOH, reflux; (ii) Ac_2O, pyridine; (iii) NaOMe, MeOH; (iv) H_2, Pd–C, HOAc/THF/H_2O, 70%.

For the one-pot synthesis of the pentasaccharide **3**, we have tried different building blocks and promoter systems, and finally we found most suitable ones. To carry out the glycosylation reaction, a variety of promoters (DMTST, NIS/TfOH, PhSCl/AgOTf, BSP/Tf_2O) were used. Nevertheless, when compound **14** or **15** was used as the second building block, we found that even the first glycosylation between **11** and **14** or **15** did not occur in the presence of any of the promoter systems. This is possibly because of the steric hindrance of the bulky group TBDPS and the electron-withdrawing effect of Bz group which decreased the activity of the 4-OH, and also because the PMB ether is sensitive to acid while the coupling condition we used are all slightly acidic.

In view of the failure of glycosylation using *N*-Troc building blocks, we turned to *N*-Phth building block **12**. We protected the 3-OH and 6-OH with benzyl group, which we expected to improve the activity of the 4-OH. The promoters mentioned above were also tried in this one-pot synthesis and BSP/Tf_2O promoted the glycosylation most efficiently. For the BSP/Tf_2O promoted one-pot operation,[14b] the donors must be activated at −70 °C and the reaction temperature was increased gradually to room temperature. The equivalent of BSP ranged from 0.5 to 1.0, and 0.5 equiv acted best. The first glycosylation between the disaccharide donor **11** and the glucosaminyl unit **12** was accomplished in 3 h to provide the trisaccharide which subsequently reacted with the lactose acceptor **13** in the second glycosylation, giving the fully protected pentasaccharide glycoside **6** (Scheme 9). The isolated yield of this BSP/Tf_2O promoted one-pot synthesis was 42%.



Scheme 9. (a) BSP, Tf_2O, CH_2Cl_2, 4 Å MS, −70 °C to rt 42%; (b) (i) $NH_2NH_2 \cdot H_2O$, EtOH, reflux; (ii) Ac_2O, pyridine; (iii) NaOMe, MeOH; (iv) H_2, Pd–C, HOAc/THF/H_2O, 43%.

Global deprotection of **6** was performed in four steps[7] (Scheme 9). The phthalimido functionality was removed with $NH_2NH_2 \cdot H_2O$ in EtOH under reflux to release the amino group and then was acetylated with acetic anhydride in pyridine. The remaining benzoylate was cleaved by the treatment with NaOMe in methanol. The benzyl, benzylidene, and benzyl carbamate functionalities were deprotected by Pd–C catalyzed hydrogenolysis. The target pentasaccharide **3** (in the form of acetate) was obtained in 43% isolated yield from **6**. The characterization of **3** and the correct anomeric configuration of each glycosidic linkage were confirmed by its 1D ^1H NMR, ^{13}C NMR and 2D correlations spectroscopy (HSQC, HMBC, TOCSY), and HRMS analysis.[15]

3. Conclusion

In summary, we have successfully synthesized the aminopropyl glycosides of two trisaccharides and a pentasaccharide which play an important role in the interaction with human anti-Gal antibodies. The protected oligosaccharides

were rapidly and efficiently synthesized by a one-pot sequential glycosylation strategy. This one-pot strategy is expected to be powerful in efficient synthesis of other α-Gal derivatives and oligosaccharides.

4. Experimental

4.1. General method

All chemicals were purchased as reagent grade and used without further purification. Dichloromethane and acetonitrile were distilled over CaH_2. Benzene was distilled over sodium/benzophenone. Methanol was distilled from magnesium. DMF was stirred with CaH_2 and distilled under reduced pressure. Reactions were monitors with analytical thin-layer chromatography on silica gel 60 F254 plates, detected under UV (254 nm) and by staining with acidic ceric ammonium molybdate. Column chromatography was performed on silica gel (200–300 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on 300 MHz Varian VXR and 500 MHz Varian INOVA spectrometer. Chemical shift (in ppm) was determined relative to tetramethylsilane in deuterated chloroform ($\delta=0$ ppm). Coupling constant are given in Hz. Mass spectra were recorded using a PE SCLEX QSTAR spectrometer. And elemental analysis data were recorded on PE-2400C elemental analyzer.

4.1.1. (3-Benzyloxycarbonylamino)propyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (16). Glucose pentaacetate (7.0 g, 0.018 mol) and benzyl *N*-(3-hydroxypropyl)-carbamate (4.5 g, 0.022 mol) were stirred in dry CH_2Cl_2 (100 mL) and $BF_3\cdot Et_2O$ (15.3 mL, 15.3 g, 0.108 mol) was added. The reaction mixture was stirred at room temperature for 8 h and then diluted with CH_2Cl_2 (100 mL), washed sequentially with satd aq $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc=1:1). The product (3.9 g, 41%) was obtained as a yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.20–7.29 (m, 5H, aromatic), 5.15–5.20 (m, 1H), 5.10 (t, $J=9.6$ Hz, 1H), 4.91–5.02 (m, 3H), 4.87 (dd, $J=8.1$, 9.3 Hz, 1H), 4.40 (d, $J=7.8$ Hz, 1H), 4.14 (dd, $J=4.5$, 12.3 Hz, 1H), 4.03 (dd, $J=2.4$, 12.0 Hz, 1H), 3.80 (dt, $J=9.9$, 5.4 Hz, 1H), 3.56–3.60 (m, 1H), 3.48 (dt, $J=9.3$, 4.4 Hz, 1H), 3.0.–3.24 (m, 2H), 1.97 (s, 3H, COCH_3), 1.94 (s, 3H, COCH_3), 1.92 (s, 3H, COCH_3), 1.89 (s, 3H, COCH_3), 1.67–1.70 (m, 2H, OCH$_2$CH_2CH$_2$N); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.5 (*C*OCH$_3$), 170.0 (*C*OCH$_3$), 169.2 (*C*OCH$_3$), 156.3 (N*C*OO), 136.4, 128.2, 127.8, 127.8 (aromatics), 100.4 (C-1), 72.5, 71.5, 71.0, 68.1, 67.3, 66.2, 61.6, 37.9 (OCH$_2$CH$_2$*C*H$_2$N), 29.2 (OCH$_2$*C*H$_2$CH$_2$N), 20.4 (CO*C*H$_3$), 20.4 (CO*C*H$_3$), 20.4 (CO*C*H$_3$); FAB-MS $(M+H)^+$ 540. Anal. Calcd for $C_{25}H_{33}O_{12}N$: C, 55.65; H, 6.16; N, 2.60. Found: C, 55.80; H, 6.19; N, 2.30.

4.1.2. (3-Benzyloxycarbonylamino)propyl 4,6-*O*-benzylidene-β-D-glucopyranoside (17). To a stirred solution of **16** (3.0 g, 5.51 mmol) in methanol (50 mL), NaOMe (0.2 mL, 30% in MeOH, 0.55 mmol) was added. The reaction mixture was stirred at room temperature for 5 h and then neutralized with cation exchange resin (H^+). The resin was filtered off and the filtrate was concentrated. The residue was suspended in dry CH_3CN (60 mL). Benzaldehyde dimethyl acetal (1.0 mL, 1.0 g, 6.61 mmol) and (±)-10-camphorsulfonic acid (0.1 g, 0.44 mmol) were added to the mixture. The reaction mixture was stirred for 5 h, then neutralized with triethylamine. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc=1:1), yielding a white glassy solid (1.7 g, 66%). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.24–7.45 (m, 10H, aromatic), 5.57 (s, 1H, benzylidene-C*H*), 5.29 (dd, $J=5.0$, 13.5 Hz, 1H), 5.01 (br.m, 2H), 4.32 (d, $J=8.0$ Hz, 1H), 4.17 (dd, $J=3.5$, 10.0 Hz, 1H), 3.73 (dt, $J=10.0$, 5.0 Hz, 1H), 3.66–3.70 (m, 1H), 3.49 (dt, $J=9.0$, 4.5 Hz, 1H), 3.16–3.20 (m, 6H), 3.09–3.06 (m, 2H), 1.70–1.65 (m, 2H, OCH$_2$CH_2CH$_2$N); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 156.1 (N*C*OO), 137. 8, 137.2, 128.8, 128.4, 128.0, 127.8, 126.3 (aromatics), 103.4, 100.6, 80.6, 74.3, 72.8, 68.0, 66.8, 65.8, 65.2, 37.5 (OCH$_2$CH$_2$*C*H$_2$N), 29.6 (OCH$_2$*C*H$_2$CH$_2$N); FAB-MS $(M+H)^+$ 460. Anal. Calcd for $C_{24}H_{29}O_8N$: C, 62.73; H, 6.36; N, 3.05. Found: C, 62.55; H, 6.38; N, 2.83.

4.1.3. (3-Benzyl-3-benzyloxycarbonylamino)propyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (18). Compound **17** (1.6 g, 3.53 mmol) and sodium hydride (0.36 mg, 14.12 mmol) were stirred in DMF (30 mL) at 0 °C for 10 min and benzyl bromide (1.7 mL, 2.4 g, 14.12 mmol) was added. The mixture was stirred at room temperature overnight and then poured into ice water (30 mL), which was extracted with EtOAc (3×30 mL), then dried (Na_2SO_4). The organic phase was concentrated for column chromatography on silica gel (petroleum ether/EtOAc=4:1). Compound **18** (2.5 g, 97%) was obtained as a yellow syrup. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.21–7.43 (m, 25H, aromatic), 5.66 (s, 1H, benzylidene-C*H*), 5.10 (br.s, 2H), 4.45–4.78 (m, 7H), 4.20 (m, 1H), 4.10 (q, $J=5.0$ Hz, 1H), 3.68–3.76 (m, 4H), 3.38–3.54 (m, 2H), 3.28 (m, 2H), 1.76 (m, 2H, OCH$_2$CH_2CH$_2$N); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 155.8 (N*C*OO), 138.7, 138.4, 138.1, 137.6, 136.9, 128.7, 128.5, 128.4, 128.0, 127.8, 127.5, 127.4, 127.4, 127.3, 127.1, 127.0, 125.9 (aromatics), 102.9, 100.0, 81.6, 80.5, 80.1, 74.0, 73.7, 67.8, 67.0, 66.9, 66.4, 65.2, 50.0, 28.4 (OCH$_2$*C*H$_2$CH$_2$N); FAB-MS $(M+H)^+$ 730. Anal. Calcd for $C_{45}H_{47}O_8N$: C, 74.05; H, 6.49; N, 1.92. Found: C, 73.91; H, 6.49; N, 1.76.

4.1.4. (3-Benzyl-3-benzyloxycarbonylamino)propyl 2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (9). To a mixture of compound **18** (2.4 g, 3.29 mmol), $NaCNBH_3$ (2.7 g, 0.041 mol), and 3 Å MS (2.5 g) in dry THF (50 mL), was added dropwise a solution of HCl–Et_2O (66 mL, 1 M in Et_2O, 65.8 mmol) under N_2 at room temperature. The mixture was stirred for 10 min, then filtered off through Celite. The filtrate was washed sequentially with satd aq $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc=3:1). The product (2.1 g, 88%) was obtained as a yellow syrup. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.23–7.32 (m, 25H, aromatic), 5.40 (d, $J=6.0$ Hz, 1H, H-1), 5.09 (br.s, 2H), 4.36–4.82 (m, 10H), 4.07–4.12 (m, 2H), 3.71–3.75 (m, 2H), 3.29–3.55 (m, 4H), 1.70–1.80 (m, 2H, OCH$_2$CH_2CH$_2$N); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.6 (N*C*OO), 138.5, 138.3, 137.8, 137.7, 136.6, 129.6, 128.9, 128.5, 128.4, 128.4, 128.3,

128.2, 127.9, 127.8, 127.8, 127.7, 127.6, 127.6, 127.2 (aromatics), 103.4 (C-1), 83.9, 81.6, 76.2, 75.2, 74.6, 74.0, 73.5, 71.4, 70.1, 67.1, 58.2, 50.6, 28.6 ($OCH_2CH_2CH_2N$); FAB-MS $(M+H)^+$ 732. Anal. Calcd for $C_{45}H_{49}O_8N$: C, 73.85; H, 6.75; N, 1.91. Found: C, 74.12; H, 6.87; N, 1.72.

4.1.5. (3-Benzyloxycarbonylamino)propyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (20). To a mixture of compound **19**[15] (100 mg, 0.17 mmol), benzyl *N*-(3-hydroxypropyl)-carbamate (48.6 mg, 0.22 mmol), and 4 Å MS (2.5 g) in dry CH_2Cl_2 (10 mL), were added NIS (39.5 mg, 0.18 mmol) and TfOH (69 μL, 0.5 M in Et_2O, 0.034 mmol) under N_2 at 0 °C. After stirred for 2 h, the mixture was neutralized with triethylamine, then filtered off through Celite. The filtrate was washed sequentially with satd aq $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 1:1). The product (56 mg, 49%) was obtained as a yellow solid. ^1H NMR (500 MHz, DMSO-d_6) δ: 7.71–7.92 (m, 4H, aromatic), 7.49 (d, J = 6.5 Hz, 2H, aromatic), 7.26–7.49 (m, 7H, aromatic), 7.07 (t, J = 5.0 Hz, 1H, aromatic), 6.97 (t, J = 7.0 Hz, 1H, aromatic), 6.87–6.92 (m, 4H, aromatic), 5.77 (s, 1H, benzylidene-C*H*), 5.14 (d, J = 8.5 Hz, 1H, H-1), 4.85 (br.s, 2H), 4.70 (d, J = 12.0 Hz, 1H), 4.40 (d, J = 12.5 Hz, 1H), 4.28–4.32 (m, 2H), 3.99 (dd, J = 8.5, 10.5 Hz, 1H), 3.98 (t, J = 9.5 Hz, 1H), 3.85 (t, J = 10.0 Hz, 1H), 3.67 (t, J = 10.0 Hz, 1H), 3.58 (dt, J = 4.5, 9.0 Hz, 1H), 3.34–3.42 (m, 2H), 3.12–3.20 (m, 1H), 2.76–2.80 (m, 2H), 1.40–1.49 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 167.4 (Phth-*C*ON), 155.9 (N*C*OO), 137.8, 137.6, 137.2, 134.7, 130.7, 128.9, 128.3, 128.2, 127.9, 127.7, 127.5, 127.4, 126.0, 123.4, 100.2, 98.3, 81.9, 74.6, 73.1, 67.8, 66.7, 65.7, 65.0, 55.4, 36.8, 29.4; FAB-MS $(M+H)^+$ 679. Anal. Calcd for $C_{39}H_{38}O_9N_2$: C, 69.01; H, 5.64; N, 4.13. Found: C, 68.95; H, 5.64; N, 3.92.

4.1.6. (3-Benzyloxycarbonylamino)propyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (10). To a mixture of compound **20** (0.44 g, 0.66 mmol), $NaCNBH_3$ (0.55 g, 8.25 mmol), and 3 Å MS (2.5 g) in dry THF (50 mL), was added dropwise a solution of HCl–Et_2O (13.2 mL, 1 M in Et_2O 13.2 mmol) under N_2 at room temperature. The mixture was stirred for 30 min, then filtered off through Celite. The filtrate was washed sequentially with satd aq $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 3:1). The product (0.4 g, 91%) was obtained as a yellow syrup. ^1H NMR (300 MHz, DMSO-d_6) δ: 7.73–7.85 (m, 4H, aromatic), 7.28–7.37 (m, 9H, aromatic), 7.07 (t, J = 5.7 Hz, 1H, aromatic), 6.86–6.94 (m, 5H, aromatic), 5.65 (d, J = 6.6 Hz, 1H), 5.03 (d, J = 11.4 Hz, 1H), 4.89 (br.s, 2H), 4.76 (d, J = 12.0 Hz, 1H), 4.57 (br.s, 2H), 4.41 (d, J = 12.3 Hz, 1H), 4.02–4.14 (m, 2H), 3.35–3.86 (m, 7H), 2.81 (q, J = 6.3 Hz, 2H), 1.41–1.53 (m, 2H, $OCH_2CH_2CH_2N$); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 167.6 (Phth-*C*ON), 167.4 (Phth-*C*ON), 155.9 (N*C*OO), 138.6, 138.3, 137.2, 134.6, 130.8, 128.3, 128.2, 127.8, 127.7, 127.4, 127.3, 127.1, 123.2 (aromatics), 97.6 (C-1), 78.6, 75.7, 73.5, 72.3, 71.6, 69.1, 66.4, 65.0, 55.2, 37.0 ($OCH_2CH_2CH_2N$), 29.4 ($OCH_2CH_2CH_2N$); FAB-MS $(M+H)^+$ 681. Anal. Calcd for $C_{39}H_{40}O_9N_2$: C, 68.81; H, 5.92; N, 4.12. Found: C, 68.80; H, 6.11; N, 3.76.

4.1.7. *p*-Methylphenyl 2-*O*-benzoyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-4,6-*O*-benzylidene-1-thio-β-D-galactopyranoside (11). Donor **7**[9a] (44.6 mg, 0.069 mmol), BSP (12 mg, 0.063 mmol), and 4 Å MS (200 mg) were stirred in dry CH_2Cl_2 (2 mL) at room temperature for 0.5 h under N_2. The mixture was cooled to −70 °C, followed by the addition of Tf_2O (11.9 μL, 19.5 mg, 0.069 mmol). After 10 min, a solution of acceptor **8**[9a] (30 mg, 0.063 mmol) in dry CH_2Cl_2 (2 mL) was added to the reaction mixture, and the temperature was increased gradually to room temperature. After 2 h, the reaction was quenched with triethylamine (2 mL) and diluted with CH_2Cl_2 (10 mL). The reaction mixture was filtered and washed sequentially with satd aq $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 3:1). The product (56 mg, 90%) was obtained as a yellow syrup. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.96 (d, J = 8.0 Hz, 2H, aromatic), 7.41–7.45 (m, 3H, aromatic), 7.34 (d, J = 7.5 Hz, 2H, aromatic), 7.02-7.27 (m, 23H, aromatic), 6.89 (d, J = 8.0 Hz, 2H, aromatic), 6.97 (d, J = 8.0 Hz, 2H, aromatic), 5.49 (t, J = 9.5 Hz, 1H, H-2), 5.32 (s, 1H, benzylidene-C*H*), 4.98 (d, J = 3.0 Hz, 1H, H-1′), 4.70 (d, J = 11.8 Hz, 1H), 4.65 (d, J = 9.5 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 4.49 (d, J = 11.5 Hz, 1H), 4.39 (d, J = 11.5 Hz, 1H), 4.35 (d, J = 12.0 Hz, 1H), 4.24–4.31 (m, 4H), 4.18 (d, J = 12.0 Hz, 1H), 3.84–3.94 (m, 3H), 3.74 (t, J = 6.0 Hz, 1H), 3.55 (d, J = 10.0 Hz, 1H), 3.34 (d, J = 13.0 Hz, 2H), 3.05–3.20 (m, 2H), 2.26 (s, 3H, SPhCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 164.6 (*C*O), 138.8, 138.7, 138.5, 138.3, 138.1, 137.7, 134.2, 132.9, 130.1, 129.8, 129.5, 128.9, 128.3, 128.2, 128.1, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 126.6 (aromatics), 101.0, 94.6, 85.4, 78.6, 75.8, 75.5, 74.9, 74.6, 74.2, 73.1, 72.2, 71.8, 69.9, 69.8, 69.3, 69.0, 68.7, 21.2 (SPh*C*H_3); TOF-MS $(M+NH_4)^+$ 1018. Anal. Calcd for $C_{61}H_{60}O_{11}S$: C, 73.17; H, 6.04. Found: C, 72.84; H, 6.17.

4.1.8. *p*-Methylphenyl 4,6-*O*-*p*-methoxybenzylidene-2-deoxy-2-(2,2,2-trichloroethoxylcarbonyl- amino)-1-thio-β-D-glucopyranoside (21). To a stirred solution of *p*-methylphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxylcarbonylamino)-1-thio-β-D-glucopyranoside[9a] (1.100 g, 1.9 mmol) in methanol (40 mL), NaOMe (13 μL, 30% in MeOH, 0.37 mmol) was added. The reaction mixture was stirred at room temperature for 6 h and then neutralized with cation exchange resin (H^+). The resin was filtered off and the filtrate was concentrated. The residue (white solid) was suspended in dry CH_3CN (40 mL). *p*-Methoxybenzaldehyde dimethyl acetal (0.63 mL, 685 mg, 3.74 mmol) and (±)-10-camphorsulfonic acid (87 mg, 0.374 mmol) were added to the mixture. The reaction mixture was stirred for 5 h then neutralized with triethylamine. The solvent was removed by rotaevaporator. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 1:2), yielding a white glassy solid (0.95 g, 90%). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.37–7.40 (m, 4H, aromatic), 7.14 (d, J = 8.1 Hz, 2H, aromatic), 6.87 (d, J = 8.7 Hz, 2H, aromatic), 5.48 (s, 1H, *p*-methyloxybenzylidene-C*H*), 5.28 (d, J = 6.0 Hz, 1H),

4.84 (d, J=10.5 Hz, 1H), 4.82 (d, J=12.0 Hz, 1H), 4.70 (d, J=12.0 Hz, 1H), 4.34 (dd, J=4.2, 10.2 Hz, 1H), 3.90–4.05 (m, 1H), 3.78 (s, 3H), 3.71–3.75 (m, 1H), 3.39–3.48 (m, 2H), 2.97 (br.s, 1H), 2.34 (s, 3H, SPhCH_3), 2.01 (d, J= 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.3, 154.3, 138.7, 134.0, 133.5, 130.2, 129.9, 129.4, 127.7, 127.4, 113.8, 101.8, 86.7, 81.1, 74.7, 72.3, 70.3, 68.5, 55.3, 21.2; MALDI-TOF-MS $(M+H)^+$ 578.

4.1.9. *p*-Methylphenyl 3-*O*-benzoyl-4,6-*O*-*p*-methoxybenzylidene-2-deoxy-2-(2,2,2-trichloro-ethoxylcarbonylamino)-1-thio-β-D-glucopyranoside (22). Compound **21** (1.03 g, 1.8 mmol) in pyridine (30.0 mL) was stirred at 0 °C and benzoyl chloride (1.0 mL, 1.00 g, 7.1 mmol) was added. After 5 h, pyridine was evaporated in vacuum and the residue was dissolved in CH_2Cl_2. The resulting pyridinium salt was filtered off, and the filtrate was concentrated. The residue was recrystallized with petroleum ether/EtOAc (1:2) to give a yellow crystal (1.02 g, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.02 (d, J=7.2 Hz, 2H, aromatic), 7.54 (t, J= 7.5 Hz, 1H, aromatic), 7.37–7.46 (m, 4H, aromatic), 7.27 (d, J=8.7 Hz, 2H, aromatic), 7.09 (d, J=7.8 Hz, 2H, aromatic), 6.73 (d, J=9.0 Hz, 2H, aromatic), 5.90 (d, J=9.9 Hz, 1H), 5.66 (t, J=9.6 Hz, 1H), 5.45 (s, 1H, *p*-methyloxybenzylidene-C*H*), 4.80 (d, J=10.5 Hz, 1H), 4.58–4.71 (ABq, J=12.3 Hz, 2H), 4.23 (dd, J=4.8, 10.2 Hz, 1H), 4.05 (q, J=10.2 Hz, 1H), 3.80 (q, J= 9.3 Hz, 2H), 3.72 (s, 3H), 3.60–3.65 (m, 1H), 2.32 (s, 3H, SPhCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.7, 160.0, 154.4, 138.4, 133.5, 133.3, 130.2, 130.0, 129.8, 129.3, 129.1, 128.5, 128.4, 127.3, 113.5, 101.2, 95.3, 88.4, 78.6, 74.4, 73.4, 70.7, 68.4, 55.2, 21.2; MALDI-TOF-MS $(M+H)^+$682. Anal. Calcd for $C_{31}H_{30}Cl_3NO_8S$: C, 54.52; H, 4.43; N, 2.05. Found: C, 54.53; H, 4.52; N, 1.92.

4.1.10. *p*-Methylphenyl 3-*O*-benzoyl-6-*O*-*p*-methoxybenzyl-2-deoxy-2-(2,2,2-trichloroethoxyl carbonylamino)-1-thio-β-D-glucopyranoside (14). Compound **22** (0.70 g, 1.0 mmol), $NaCNBH_3$ (0.34 g, 5.2 mmol), and 4 Å MS (1.25 g) were stirred in dry DMF (10.0 mL) at room temperature for 0.5 h under N_2. Then the reaction mixture was cooled to 0 °C, a solution of trifluoroacetic acid (0.77 mL, 1.17 g, 10.3 mmol) in dry DMF (7.0 mL) was added dropwise. The reaction temperature was increased to room temperature in 1.5 h. After another 11 h of stirring, the reaction mixture was filtered and the filtrate was diluted with H_2O (100 mL), extracted with EtOAc (3×50 mL), then dried (Na_2SO_4). The organic phase was concentrated for column chromatography on silica gel (petroleum ether/ EtOAc=2:1). Compound **14** (0.57 g, 80%) was obtained as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.03 (d, J=9.6 Hz, 1H, aromatic) 7.90 (d, J=7.2 Hz, 2H, aromatic), 7.63 (t, J=7.2 Hz, 1H, aromatic), 7.49 (t, J=7.8 Hz, 2H, aromatic), 7.36 (d, J=8.1 Hz, 2H, aromatic), 7.24 (d, J= 8.4 Hz, 2H, aromatic), 7.07 (d, J=8.4 Hz, 2H, aromatic), 6.90 (d, J=8.7 Hz, 2H, aromatic), 5.61 (d, J=5.4 Hz, 1H), 5.20 (t, J=9.3 Hz, 1H), 4.91 (d, J=10.5 Hz, 1H), 4.80 (d, J=12.6 Hz, 1H), 4.58 (d, J=12.9 Hz, 1H), 4.35–4.47 (m, 2H), 3.26–3.70 (m, 8H), 2.26 (s, 3H, SPhCH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 165.2, 158.7, 154.1, 136.8, 133.2, 131.2, 130.5, 129.8, 129.7, 129.6, 129.4, 129.1, 128.5, 113.6, 96.0, 85.4, 79.4, 77.4, 73.1, 72.0, 69.0, 68.1, 55.0, 54.7, 20.6; MALDI-TOF-MS $(M+NH_4)^+$701. Anal. Calcd for $C_{31}H_{32}Cl_3NO_8S$: C, 54.36; H, 4.71; N, 2.04. Found: C, 54.27; H, 4.82; N, 2.00.

4.1.11. *p*-Methylphenyl 3-*O*-benzoyl-2-deoxy-2-(2,2,2-trichloroethoxyl carbonylamino)-1-thio-β-D-glucopyranoside (23). Compound **22** (40.8 mg, 0.06 mmol) was stirred in acetic acid (80%, 2.0 mL) at room temperature overnight. After removal of the solvent, the residue was purified by column chromatography on silica gel (petroleum ether/EtOAc=1:1), yielding a colorless solid (29.7 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.95 (d, J=7.2 Hz, 2H, aromatic), 7.53 (t, J=7.5 Hz, 1H, aromatic), 7.33–7.38 (m, 4H, aromatic), 7.08 (d, J=7.2 Hz, 2H, aromatic), 5.61 (d, J=9.3 Hz, 1H), 5.34 (t, J=9.3 Hz, 1H), 4.79 (d, J=10.5 Hz, 1H), 4.69 (d, J=12.0 Hz, 1H), 4.53 (d, J=12.3 Hz, 1H), 3.53–3.96 (m, 4H), 3.49–3.52 (m, 1H), 2.67 (br, 2H), 2.31 (s, 3H, SPhCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.4, 154.3, 138.4, 133.7, 132.9, 130.0, 129.8, 128.9, 128.5, 95.3, 87.2, 79.4, 74.3, 69.3, 62.3, 55.0, 21.2.

4.1.12. *p*-Methylphenyl 3-*O*-benzoyl-6-*O*-*tert*-butyldiphenylsilyl-2-deoxy-2-(2,2,2-trichloroethoxyl carbonylamino)-1-thio-β-D-glucopyranoside (15). To a solution of **23** (1.60 g, 2.9 mmol) in DMF (10.0 mL), *tert*-butyldiphenylsilyl chloride (1.5 mL, 1.60 g, 5.7 mmol) and imidazole (0.50 g, 7.2 mmol) were added. The mixture was stirred overnight. After removal of the solvent, the residue was purified by column chromatography on silica gel (petroleum ether/EtOAc=3:1), yielding a yellow solid (1.90 g, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.00 (d, J = 7.2 Hz, 2H, aromatic) 7.66–7.71 (m, 4H, aromatic), 7.54 (t, J=7.2 Hz, 1H, aromatic), 7.24–7.42 (m, 10H, aromatic), 7.03 (d, J= 8.1 Hz, 2H, aromatic), 5.32 (t, J=9.0 Hz, 2H), 4.73 (d, J= 10.5 Hz, 1H), 4.71 (d, J=12.0 Hz, 1H), 4.53 (d, J= 12.3 Hz, 1H), 3.83–3.97 (m, 5H), 3.51–3.56 (m, 1H), 2.30 (s, 3H, SPhCH_3), 1.05 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.3, 154.1, 138.2, 135.7, 135.6, 133.6, 133.0, 132.8, 132.7, 130.1, 129.9, 129.7, 129.1, 128.4, 95.3, 87.3, 79.3, 74.4, 70.5, 64.3, 54.8, 26.8, 21.2, 19.2; MALDI-TOF-MS $(M+H)^+$ 802.

4.1.13. (3-Benzyl-3-benzyloxycarbonylamino)propyl 2,3,6-tri-*O*-benzyl-4-*O*-[2-*O*-benzoyl-3-*O*-(2, 3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-4,6-*O*-benzylidene-β-D-galactopyranosyl]-β-D-glucopyranoside (4). Building block **7** (0.16 g, 0.25 mmol), building block **8** (0.10 g, 0.21 mmol), and 4 Å MS (0.50 g) were stirred in dry CH_2Cl_2 (10.0 mL) at 0 °C under N_2, which was followed by the addition of NIS (0.13 g, 0.25 mmol) and TfOH (42 μL, 0.5 M in Et_2O, 0.015 mmol). After stirred for 0.5 h, TLC (petroleum ether/acetone=3:2) showed complete consumption of building block **8**. Then building block **9** (0.23 g, 0.31 mmol), NIS (0.13 g, 0.25 mmol), and TfOH (42 μL, 0.5 M in Et_2O, 0.015 mmol) were added to the reaction mixture. The reaction mixture was stirred for 3 h and quenched with triethylamine, then filtered off through Celite. The filtrate was washed sequentially with satd aq $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/acetone=4:1). The product (175 mg, 55%) was obtained as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.94 (d, J=7.5 Hz, 2H, aromatic), 7.61 (t, J=7.5 Hz, 1H, aromatic), 7.10–7.41 (m, 52H,

aromatic), 5.54 (s, 1H, benzylidene-C*H*), 5.34 (dd, $J=8.5$, 10.0 Hz, 1H), 5.29 (d, $J=3.0$ Hz, 1H, H-1″), 5.06 (br.s, 3H), 4.82 (d, $J=7.5$ Hz, 1H), 4.18–4.72 (m, 17H), 3.93–4.03 (m, 3H), 3.72–3.79 (m, 4H), 3.40–3.50 (m, 6H), 3.16–3.28 (m, 7H), 1.66–1.82 (m, 2H, $OCH_2CH_2CH_2N$); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 164.5, 139.1, 138.6, 138.5, 138.2, 138.1, 136.9, 133.6, 129.4, 129.0, 128.7, 128.4, 128.3, 128.23, 128.17, 128.1, 128.0, 127.8, 127.7, 127.5, 127.4, 127.3, 127.2, 127.1, 127.0, 126.2, 102.0, 100.3, 99.8, 93.1, 82.1, 81.2, 77.7, 77.2, 75.1, 74.4, 74.2, 74.0, 73.6, 73.4, 73.3, 72.4, 72.1, 71.9, 71.1, 70.7, 68.9, 68.2, 68.1, 66.3, 66.2, 49.9, 43.6, 39.0, 29.0; MALDI-TOF-MS $(M+Na)^+$ 1630, $(M+K)^+$ 1646. Anal. Calcd for $C_{99}H_{101}O_{19}N$: C, 73.90; H, 6.33; N, 0.87. Found: C, 73.66; H, 6.53; N, 0.56.

4.1.14. 3-Aminopropyl 4-*O*-[3-*O*-(α-D-galactopyranosyl)-β-D-galactopyranosyl]-β-D-glucopyranoside (1). Compound **4** (60.0 mg, 0.037 mmol) was dissolved in methanol (5.0 mL), and to this NaOMe (30% in MeOH, 10 μL) was added. The mixture was stirred for 6 h and then neutralized with cation exchange resin (H^+). The resin was filtered off and the filtrate was evaporated in vacuum. The residue was purified by silica gel column chromatography (petroleum ether/acetone=4:1). A mixture of the purified residue, 10% Pd–C (15.0 mg) in HOAc (4 mL), THF (2 mL), H_2O (1 mL) was stirred under H_2 atmosphere for 24 h. The catalyst was then removed by filtration and the filtrate was concentrated. The residue was subjected to a C-18 reverse phase column chromatography (H_2O) to give **1** (14.6 mg, 70%) as a white solid after lyophilization. ^1H NMR (500 MHz, D_2O) δ: 5.13 (d, $J=3.5$ Hz, 1H, H-1″), 4.51 (d, $J=8.0$ Hz, 1H), 4.50 (d, $J=8.0$ Hz, 1H), 4.16–4.20 (m, 2H), 3.90–4.10 (m, 4H), 3.69–3.89 (m, 8H), 3.55–3.69 (m, 4H), 3.15 (t, $J=7.0$ Hz, 2H, $OCH_2CH_2CH_2N$), 1.98–2.05 (m, 2H, $OCH_2CH_2CH_2N$); ^{13}C NMR (125 MHz, D_2O) δ: 182.1, 103.6, 102.8, 96.2 (C-1″), 79.4, 77.9, 75.8, 75.5, 75.2, 73.5, 71.6, 70.3, 70.0, 69.9, 68.9, 68.6, 65.5, 61.7, 61.6, 60.8, 38.3 ($OCH_2CH_2CH_2N$), 27.4 ($OCH_2CH_2CH_2N$), 23.9; HRMS (M+Na) calcd for $C_{21}H_{39}O_{16}NNa$ 584.2167, found 584.2168.

4.1.15. (3-Benzyloxycarbonylamino)propyl 3,6-di-*O*-benzyl-4-*O*-[2-*O*-benzoyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-4,6-*O*-benzylidene-β-D-galactopyranosyl]-2-deoxy-2-phthalimido-β-D-glucopyranoside (5). Building block **7** (0.82 g, 1.25 mmol), building block **8** (0.50 g, 1.05 mmol), and 4 Å MS (1.00 g) were stirred in dry CH_2Cl_2 (30.0 mL) at 0 °C under N_2, which was followed by the addition of NIS (0.66 g, 1.25 mmol) and TfOH (0.21 mL, 0.5 M in Et_2O, 0.105 mmol). After stirred for 0.5 h, TLC (petroleum ether/acetone=3:2) showed complete consumption of building block **8**. Then building block **10** (1.20 g, 1.58 mmol), NIS (0.66 g, 1.25 mmol), and TfOH (0.21 mL, 0.5 M in Et_2O, 0.105 mmol) were added to the reaction mixture. The reaction mixture was stirred for 3 h and quenched with triethylamine, then filtered off through Celite. The filtrate was washed sequentially with satd aq $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/acetone=4:1). The product (814.0 mg, 55%) was obtained as a yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ: 8.00 (d, $J=7.5$ Hz, 2H, aromatic), 7.60–7.65 (m, 2H, aromatic), 7.51 (t, $J=7.5$ Hz, 1H, aromatic), 7.10–7.38 (m, 39H, aromatic), 6.97 (dd, $J=2.0$, 7.5 Hz, 2H, aromatic), 6.72–6.80 (m, 3H, aromatic), 5.64 (dd, $J=8.5$, 10.0 Hz, 1H, H-2′), 5.31 (s, 1H, benzylidene-C*H*), 4.96–5.06 (m, 6H), 4.79 (d, $J=11.5$ Hz, 1H), 4.72 (d, $J=8.5$ Hz, 1H), 4.50–4.63 (m, 5H), 4.44 (d, $J=12.0$ Hz, 1H), 4.21–4.38 (m, 7H), 4.04–4.12 (m, 4H), 3.97 (dd, $J=3.5$, 10 Hz, 1H), 3.83–3.92 (m, 2H), 3.81 (dd, $J=3.5$, 10.0 Hz,1H), 3.67–3.72 (m, 3H), 3.51–3.55 (m, 2H), 3.38–3.41 (m, 2H), 3.27 (dd, $J=7.0$, 9.0 Hz, 1H), 3.15–3.18 (m, 1H), 2.98–3.02 (m, 1H), 1.65–1.74 (m, 2H, $OCH_2CH_2CH_2N$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.7, 164.7, 156.3, 138.7, 138.68, 138.6, 138.5, 138.3, 138.1, 137.8, 136.7, 133.6, 133.1, 131.6, 130.9, 129.8, 128.7, 128.44, 128.4, 128.3, 128.2, 128.14, 128.1, 128.0, 127.9, 127.8, 127.78, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 126.8, 126.3, 123.2, 101.1, 100.8, 98.2, 95.8, 78.5, 78.2, 75.8, 75.3, 75.1, 74.9, 74.7, 74.6, 73.2, 73.2, 73.1, 72.3, 72.2, 71.3, 69.9, 68.9, 68.6, 67.8, 66.6, 66.4, 66.3, 65.5, 58.4, 55.6, 37.7, 29.1; TOF-MS $(M+NH_4)^+$ 1574. Anal. Calcd for $C_{93}H_{92}O_{20}N_2$: C, 71.71; H, 5.95; N, 1.80. Found: C, 71.49; H, 5.89; N, 1.55.

4.1.16. 3-Aminopropyl 4-*O*-[3-*O*-(α-D-galactopyranosyl)-β-D-galactopyranosyl]-2-acetamido-2-deoxy-β-D-glucopyranoside (2). Compound **5** (44.0 mg, 0.028 mmol) was dissolved in EtOH (3.0 mL) and treated with $NH_2NH_2\cdot H_2O$ (1.0 mL). The mixture was heated under reflux for 24 h, it was then concentrated under reduced pressure and the residue was co-evaporated with toluene (3×5 mL). The crude product was dissolved in pyridine (3.0 mL) and acetic anhydride (1.0 mL). After stirring for 8 h, the solvent was removed in vacuum. The residue was dissolved in methanol (3.0 mL), and NaOMe (30% in MeOH, 10 μL) was added. The mixture was stirred for 6 h and then neutralized with cation exchange resin (H^+). The resin was filtered off and the filtrate was evaporated in vacuum. The residue was purified by silica gel column chromatography (petroleum ether/acetone=4:1). A mixture of the purified residue, 10% Pd–C (15.0 mg) in HOAc (4.0 mL), THF (2.0 mL), H_2O (1.0 mL) was stirred under H_2 atmosphere for 24 h. The catalyst was then removed by filtration and the filtrate was concentrated. The residue was subjected to a C-18 reverse phase column chromatography (H_2O) to give **2** (12.0 mg, 70%) as a white solid after lyophilization. ^1H NMR (500 MHz, D_2O) δ: 5.14 (d, $J=3.0$ Hz, 1H, H-1″), 4.54 (d, $J=8.0$ Hz, 1H), 4.52 (d, $J=8.0$ Hz, 1H), 4.15–4.21 (m, 2H), 3.97–4.40 (m, 3H), 3.94 (dd, $J=3.0$, 10 Hz, 1H), 3.63–3.88 (m, 12H), 3.58–3.63 (m, 2H), 3.08 (t, $J=7.0$ Hz, 2H, $OCH_2CH_2CH_2N$), 2.04 (s, 3H, CH_3CON), 1.92–1.97 (m, 2H, $OCH_2CH_2CH_2N$); ^{13}C NMR (125 MHz, D_2O) δ: 175.4 (CH_3CON), 103.6, 101.9, 96.2 (C-1″), 79.4, 77.9, 75.8, 75.4, 73.0, 71.6, 70.3, 70.0, 69.9, 68.9, 68.7, 65.5, 61.7, 61.6, 60.8, 55.8, 38.6 ($OCH_2CH_2CH_2N$), 27.4 ($OCH_2CH_2CH_2N$), 24.0, 22.9; HRMS (M+Na) calcd for $C_{23}H_{42}O_{16}N_2Na$ 625.2432, found 625.2439.

4.1.17. (3-Benzyl-3-benzyloxycarbonylamino)propyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,4,6-tri-*O*-benzyl-3-*O*-{3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-4-*O*-[2-*O*-benzoyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-4,6-*O*-benzylidene-β-D-galactopyranosyl]-β-D-glucopyranosyl}-β-D-galactopyranosyl)-β-D-glucopyranoside (6). Building block **11** (30.0 mg, 0.030 mmol), building block

12[15] (21.5 mg, 0.036 mmol), BSP (2.9 mg, 0.015 mmol), and 4 Å MS (0.20 g) were stirred in dry CH_2Cl_2 (2.0 mL) at room temperature for 0.5 h under N_2. The mixture was cooled to −70 °C, followed by the addition of Tf_2O (3.1 μL, 5.1 mg, 0.018 mmol), then warmed gradually to room temperature. After 3 h, the donor was consumed and the reaction temperature was cooled to −70 °C again, to add a solution of building block **13**[15] (45.0 mg, 0.039 mmol) and BSP (2.9 mg,, 0.015 mmol) in dry CH_2Cl_2 (2.0 mL). Subsequently Tf_2O (3.1 μL, 5.1 mg, 0.018 mmol) was added to the reaction mixture which was then warmed gradually to room temperature. After 3 h, the reaction was quenched with triethylamine (2.0 mL) and diluted with CH_2Cl_2 (10.0 mL). The reaction mixture was filtered and washed sequentially with satd aq $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 3:1). The product (31.4 mg, 42%) was obtained as a yellow syrup. Saccharide **6** was spectrometrically identical to an authentic sample prepared previously.[15]

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Steric effects in the tetracyanoethylene catalysed methanolysis of some cyclohexane epoxides

Cavit Uyanik,[a,*] James R. Hanson,[b] Peter B. Hitchcock[b] and Meredith A. Lazar[b]

[a]*Department of Chemistry, Kocaeli University, Izmit 41300, Kocaeli, Turkey*
[b]*Department of Chemistry, University of Sussex, Brighton, Sussex BN1 9QJ, UK*

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Abstract—The presence of a hydroxyl group has been shown to direct the regiochemistry and stereochemistry of the TCNE methanolysis of cyclohexane hydroxy-epoxides. α-Pinene epoxide underwent cleavage to form the 8-methyl ether of *trans*-sobrerol.

1. Introduction

Tetracyanoethylene (TCNE) is a mild π-acid catalyst which has proved to be of value in the ring opening of epoxides.[1,2] The stereochemistry of the reaction has been examined in the steroid series where neighbouring group participation by an adjacent *cis* hydroxyl group has been observed.[3] Thus, a 5β-hydroxyl group has been shown to affect both the regiochemistry and stereochemistry of the cleavage of an adjacent 3β,4β-epoxide. Whereas the TCNE catalysed methanolysis of 17β-acetoxy-3β,4β-epoxy-5β-androstane gave the diaxial 3β-hydroxy-4α-methyl ether, methanolysis of 5β-17β-dihydroxy-3β,4β-epoxy-5β-androstane gave the diequatorial 3α-methoxy-4β,5β,17β-trihydroxy-5β-androstane. In this paper, we describe the results of the TCNE catalysed methanolysis of some cyclohexane and monoterpenoid epoxides.

The first compounds to be examined were the isomeric *cis*-2,3-epoxy-1,5,5-trimethylcyclohexan-1-ol **3**[4] and *cis*-1,2-epoxy-1,5,5-trimethylcyclohexan-3-ol **5** in which the methyl groups provide a conformational 'lock'.

2. Results and discussion

The epoxides **3** and **5** were prepared from the readily available isophorone **1**. Treatment of isophorone epoxide with hydrazine hydrate gave 1,5,5-trimethylcyclohex-2-en-1-ol **2**.[5] This was epoxidized with *m*-chloroperbenzoic acid to afford *cis*-2,3-epoxy-1,5,5-trimethylcyclohexan-1-ol **3**. Reduction of **1** with sodium borohydride in methanol followed by epoxidation of the alcohol **4** with *m*-chloroperbenzoic acid, gave *cis*-1,2-epoxy-1,5,5-trimethylcyclohexan-3-ol **5**. The *cis* relationship of the epoxide and hydroxyl groups followed from the known[6] directing effect of an allylic hydroxyl group on the epoxidation of an adjacent alkene.

Methanolysis of *cis*-1,2-epoxy-1,5,5-trimethylcyclohexan-3-ol **5**, catalysed by TCNE gave a single product, *cis*-2,3-dihydroxy-*trans*-1-methoxy-1,5,5-trimethylcyclohexane **6**. The stereochemistry of the product was unambiguously established by X-ray crystallography as shown in Figure 1.

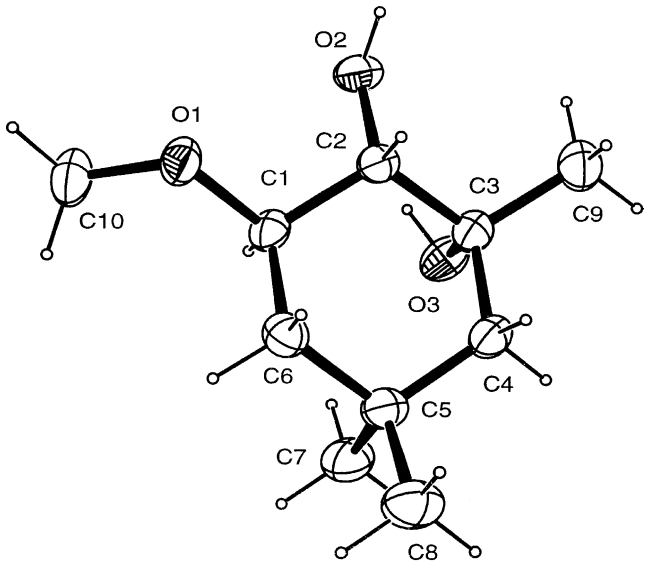

Figure 1. X-ray structure of **6**.

Keywords: Cyclohexane; TCNE; Methanoloysis; Epoxide; Stereochemistry.
* Corresponding author. Tel.: +90 262 3249910; fax: +90 262 3313906; e-mail: cuyanik@kou.edu.tr

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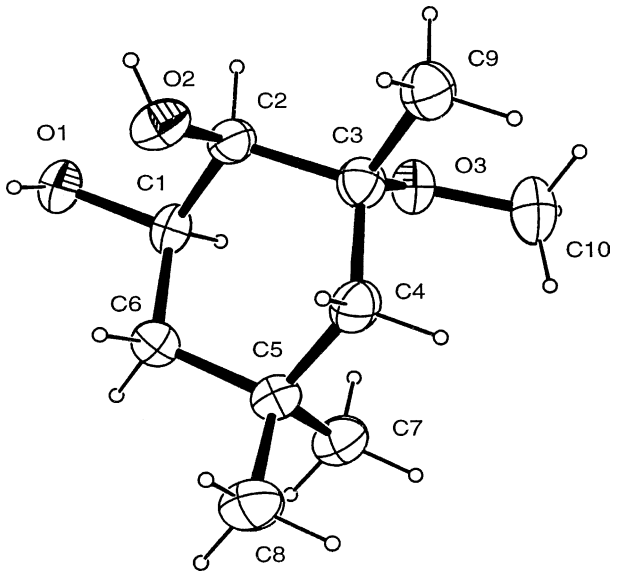


Figure 2. X-ray structure of **7**.

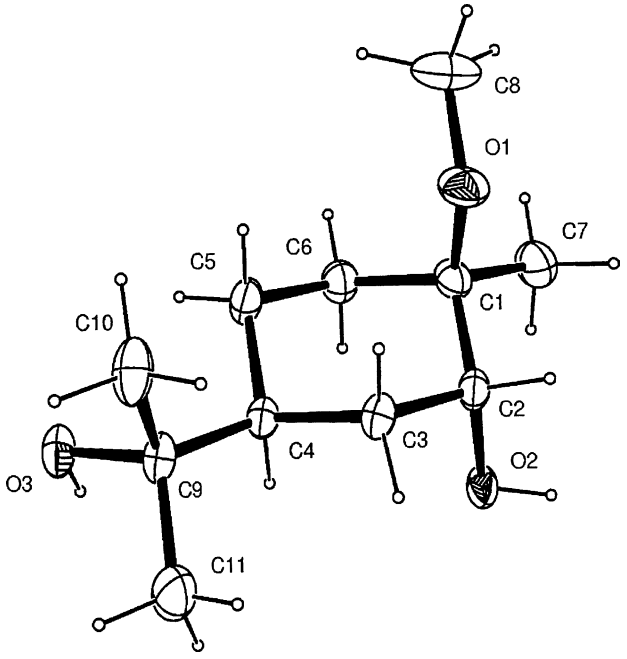
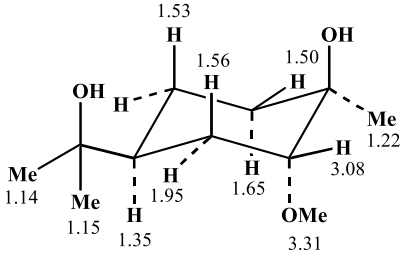


Figure 3. X-ray structure of **13**.

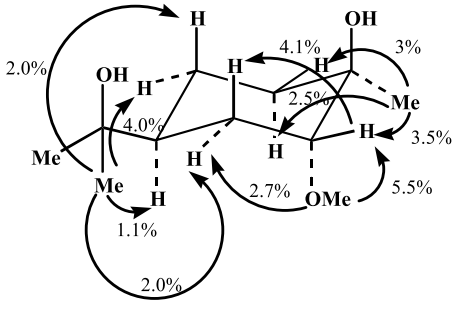
Methanolysis of the isomeric *cis*-2,3-epoxy-1,5,5-trimethylcyclohexan-1-ol **3**, catalysed by TCNE, gave *cis*-1,2-dihydroxy-*trans*-3-methoxy-1,5,5-trimethylcyclohexane **7**. In the ^{1}H NMR spectrum, the H-2 resonance (δ_H 3.19) was a doublet ($J=9.2$ Hz) whilst the H-3 resonance (δ_H 3.46) was a triplet ($J=9.2$ Hz) of doublets ($J=4.1$ Hz) consistent with a diaxial relationship between H-2 and H-3. The regiochemistry of the hydroxyl and methoxyl groups was established by X-ray crystallography as shown in Figure 2.

Whereas the methanolysis of the epoxide **5** proceeded in a diaxial sense to give **6**, that of epoxide **3** led to an eventual diequatorial relationship between the hydroxyl and methoxyl groups **7**. In both cases, the hydroxyl group arising from the epoxide is adjacent to the original hydroxyl group. The overall diequatorial opening of *cis*-2,3-epoxy-1,5,5-trimethylcyclohexan-1-ol **3** may arise via a diaxial opening and conformational inversion of the ring to maximize the number of equatorial substituents. This contrasts with the formation of the diaxial 1,2-diol **9** which is obtained[7] from 1,5,5-trimethylcyclohex-2-ene **8** on treatment with hydrogen peroxide and formic acid, a reaction which proceeds through the 1,2-epoxide. Hence the hydroxyl group of a hydroxy-epoxide has determined the regio- and stereochemistry of the methanolysis of the epoxide catalysed by TCNE.

The participation of the 8-hydroxyl group of 1,2-epoxy-8-hydroxy-*p*-menthane in the acid catalysed hydrolysis of the 1,2-epoxide leading to the formation of 2-hydroxy-1,8-cineole has been described previously.[8] We have examined the TCNE catalysed methanolysis of the mixed epoxides **10** of α -terpineol in the light of this transannular participation of a hydroxyl group. Three major products were separated by chromatography. The first was identified from its ^{1}H NMR spectrum as *trans*-2-hydroxy-1,8-cineole **11**.[8] The second product, **12**, contained a methoxyl group (δ_H 3.29) and a further ether CHOR signal (δ_H 3.05) together with three C-methyl group resonances (δ_H 1.14, 1.15 and 1.20). The CHOR resonance was a narrow signal (w/2 c.4 Hz). The stereochemistry of the compound was assigned on the basis of this signal[9] and from the nuclear Overhauser effect enhancements arising from irradiation of the methyl group signals at δ_H 1.14/1.15, 1.22 and 3.29. The assignments and NOE. enhancements are summarized in Figure 4. The structure of the third compound, **13**, which was crystalline,

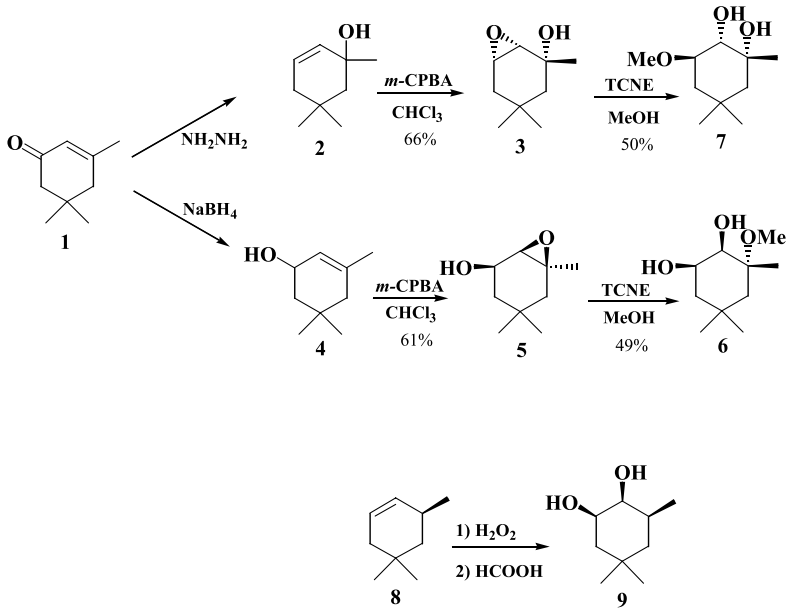


^{1}H NMR assigments for 12

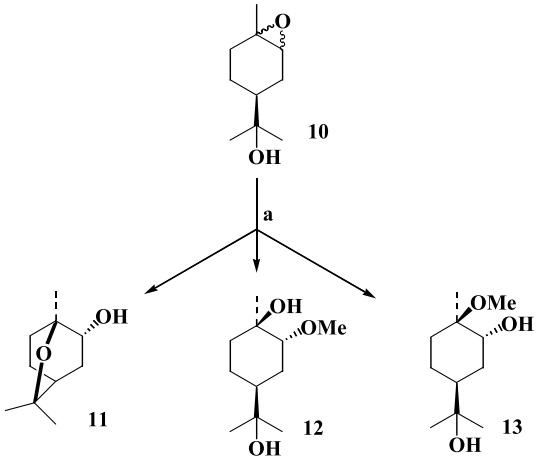


^{1}H NMR nOe enhancements for 12

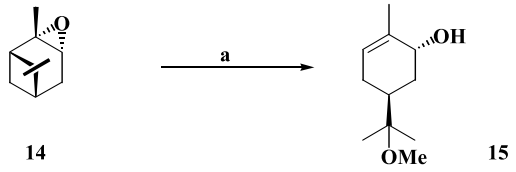
Figure 4.



Scheme 1.



Scheme 2. Reagents and conditions: (a) TCNE, MeOH, rt, 12 h.



Scheme 3. Reagents and conditions: (a) TCNE, MeOH, rt, 2 h.

was established by X-ray crystallography as shown in Figure 3. The isolation of these compounds can be rationalized in terms of the diaxial opening of the epimeric terpineol epoxides but with rather less participation of the 8-hydroxyl group in 1,8-cineole formation than is the case in simple acid-catalysed hydrolysis.[8]

Treatment of α-pinene oxide **14** with TCNE in methanol gave one major product. This compound, **15**, had the ^{1}H NMR characteristics of the 8-monomethyl ether of *trans*-sobrerol [δ_H 1.09 (6H, s, 2×Me), 1.76 (3H, br s, =C.Me), 3.17 (3H, s, OMe), 3.61(1H, br s, CHOH), 3.99 (1H, br s, =CH)] (Schemes 1–3).

3. Conclusion

We have shown that the regiochemistry and stereochemistry of the TCNE catalyzed methanolysis of some cyclohexane epoxides have been directed by the presence of a hydroxyl group. We have established the stereochemistry of the products by X-ray crystallography. The structures of these products indicate that when TCNE is used as a mild π-acid catalyst for the cleavage of hydroxy-epoxides, the hydroxyl group can participate in the reaction.

4. Experimental

4.1. General

Light petroleum refers to the fraction bp 60–80 °C. Silica for chromatography was Merck 9385. Extracts were dried over anhydrous sodium sulfate. IR spectra were determined as nujol mulls. ^{1}H NMR spectra were determined for solutions in deuteriochloroform at 300 MHz. High-resolution mass spectra were obtained on a Bruker Daltonics Apex III mass spectrometer operating in the electrospray mode.

4.1.1. *cis*-1,2-Epoxy-1,5,5-trimethycyclohexan-3-ol (5). A suspension of *m*-chloroperbenzoic acid (4 g, 23.2 mmol) in chloroform (20 cm^3) was added over 15 min to the alcohol **4** (1.5 g, 10.7 mmol) (prepared by the reduction of isophorone **1** with sodium borohydride in methanol) in chloroform (20 cm^3). The mixture was left at room temperature overnight and then diluted with chloroform (50 cm^3). The solution was stirred with aqueous acidic iron (II) sulfate (100 cm^3) twice and then the chloroform layer was washed thoroughly with aqueous sodium hydrogen carbonate, water

and dried. The solvent was evaporated to give a residue which was distilled at 70–80 °C (12 mm Hg) to give *cis*-1,2-epoxy-1,5,5-trimethycyclohexan-3-ol **5** (1.03 g, 61%) as a colourless oil; ν_{max} (Nujol) 3421 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.91 (1H, m, 3-H), 3.10 (1H, d, $J=3.5$ Hz, 2-H), 1.83–1.65 (4H, m, $2\times CH_2$), 1.30 (3H, s, 1-Me), 1.11 and 0.80 (each 3H, s, 5-Me_2); δ_C (75.4 MHz, $CDCl_3$) 78.4, 61.7, 58.6, 46.8, 44.9, 29.9, 28.2, 27.5, 26.3; HRMS: M^+, found 156.1158. $C_9H_{16}O_2$ requires 156.1150.

4.1.2. *cis*-2,3-Epoxy-1,5,5-trimethylcyclohexan-1-ol (3). Under similar conditions 1,5,5-trimethylcyclohex-2-en-1-ol **2** (1.53 g, 10.9 mmol) (prepared by the reaction of isophorone epoxide with hydrazine hydrate), gave *cis*-2,3-epoxy-1,5,5-trimethylcyclohexan-1-ol **3** (1.13 g, 66%) as a colourless oil; ν_{max} (Nujol) 3443 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.33 (1H, q, $J=3.5$ Hz, 3-H), 2.98 (1H, d, $J=3.5$ Hz, 2-H), 1.75–1.60 (4H, m, $2\times CH_2$), 1.31 (3H, s, 1-Me), 1.14 and 0.83 (each 3H, s, 5-Me_2); δ_C (75.4 MHz, $CDCl_3$) 72.7, 59.5, 57.6, 47.6, 41.4, 33.8, 30.6, 28.1, 27.4; HRMS: M^+, found 156.1158. $C_9H_{16}O_2$ requires 156.1150.

4.1.3. *cis*-1,2-Dihydroxy-*trans*-3-methoxy-1,5,5-trimethylcyclohexane (7). *cis*-2,3-Epoxy-1,5,5-trimethylcyclohexan-1-ol **3** (1.0 g, 6.4 mmol) in dry methanol (20 cm^3) was treated with tetracyanoethylene (200 mg, 1.5 mmol) at room temperature for 3 h. The solvent was evaporated and the residue was chromatographed on silica. Elution with 30% ethyl acetate: light petroleum gave *cis*-1,2-dihydroxy-*trans*-3-methoxy-1,5,5-trimethylcyclohexane **7** (600 mg, 50%) which was crystallized from ethyl acetate as needles; mp 78–79 °C; (Found: C, 63.8; H, 10.7. $C_{10}H_{20}O_3$ requires C, 63.8; H, 10.7%); ν_{max} (Nujol) 3453, 3350 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.46 (1H, td, $J=9.2$, 4.1 Hz, 3-H), 3.40 (3H, s, 3-OMe), 3.19 (1H, d, $J=9.2$ Hz, 2-H), 1.85–1.64 (4H, m, $2\times CH_2$), 1.25 (3H, s, 1-Me), 1.15 and 0.94 (each 3H, s, 5-Me_2); δ_C (75.4 MHz, $CDCl_3$) 78.9, 78.8, 72.7, 56.4, 48.3, 41.3, 33.9, 31.4, 28.8, 27.2.

4.1.4. *cis*-2,3-Dihydroxy-*trans*-1-methoxy-1,5,5-trimethylcyclohexane (6). Under similar conditions *cis*-1,2-epoxy-1,5,5-trimethylcyclohexan-3-ol **5** (900 mg, 5.7 mmol) gave, after chromatography on silica and elution with 30% ethyl acetate: light petroleum, *cis*-2,3-dihydroxy-*trans*-1-methoxy-1,5,5-trimethylcyclohexane **6** (540 mg, 49%) which was crystallized from ethyl acetate as needles, mp 65–68 °C, ν_{max} (Nujol) 3355 (br) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.17 (1H, dt, $J=9.2$, 3.5 Hz, 3-H), 3.58 (1H, d, $J=3.5$ Hz, 2-H), 3.17 (3H, s, 1-OMe), 1.89–1.61 (4H, m, $2\times CH_2$), 1.22 (3H, s, 1-Me), 1.04 and 0.93 (each 3H, s, 5-Me_2); δ_C (75.4 MHz, $CDCl_3$) 78.8, 78.6, 73.5, 51.4, 47.6, 44.2, 31.3, 30.9, 28.6, 27.2; HRMS: M^+, found 188.1410. $C_{10}H_{20}O_3$ requires 188.1412.

4.1.5. Reaction of menthanes. The mixed 1,2-epoxy-8-hydroxy-*p*-menthanes (50:50) (900 mg, 5.3 mmol) in methanol (50 cm^3) containing TCNE (100 mg, 0.78 mmol) was left at room temperature overnight. The solvent was evaporated in vacuo and the residue was chromatographed on silica. Elution with a gradient of increasing amounts of ethyl acetate in light petroleum gave *trans*-2-hydroxy-1,8-cineole **11** (105 mg, 12%) as a colourless oil; ν_{max}(Nujol) 3450 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.72 (1H, m), 3,63 (1H, br. s), 2.52–1.20 (7H, overlapping multiplets), 1.25 (3H, s, Me), 1.17 (3H, s, Me), 1.08 (3H, s, Me).[8]

Further elution gave 1β,8-dihydroxy-2α-methoxy-*p*-menthane **12** (228 mg, 21%) as a colourless oil; ν_{max} (Nujol) 3398 (br) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.05 (1H, br. s, *w*/2 4 Hz), 3.29 (3H, s, OMe), 1.94–1.09 (8H, overlapping multiplets), 1.20 (3H, s, Me), 1.15 (3H, s, Me), 1.14 (3H, s, Me); HRMS: M^+, found 225.1461. $C_{11}H_{22}O_3Na$ requires 225.1457.

Further elution gave 2α,8-dihydroxy-1β-methoxy-*p*-menthane **13** (262 mg, 24%) as needles; mp 65–68 °C; ν_{max} (Nujol) 3367, 3335 (br) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.44 (1H, s), 2.84 (3H, s, OMe), 2.20–0.74 (8H, overlapping multiplets), 1.29 (3H, s, Me), 0.97 (3H, s, Me), 0.95 (3H, s, Me); HRMS: M^+, found 225.1460. $C_{11}H_{22}O_3Na$ requires 225.1456.

4.1.6. Reaction of 14. α-Pinene oxide **14** (500 mg, 3.24 mmol) in methanol (30 cm^3) was treated with TCNE (50 mg, 0.39 mmol) at room temperature for 2 h. The solvent was evaporated in vacuo and the residue was chromatographed on silica. Elution with 10% ethyl acetate/light petroleum gave 8-methoxy-*p*-menth-6-en-2α-ol **15** (*trans*-sobrerol 8-methyl ether) (192 mg, 32%) as a colourless oil; ν_{max} (Nujol) 3413, 1643 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.99 (1H, br.s), 3.61 (1H, s), 3.17 (3H, s, OMe), 2.05–1.50 (5H, overlapping multiplets), 1.76 (3H, s, Me), 1.09 (6H, s, Me_2); HRMS: M^+, found 391.2810. $(C_{11}H_{20}O_2)_2Na$ requires 391.2810.

4.2. X-ray analysis

4.2.1. *cis*-2,3-Dihydroxy-*trans*-1-methoxy-1,5,5-trimethylcyclohexane (6). $C_{10}H_{20}O_3$, M_r 188.26, monoclinic, $P2_1/n$ (no. 14), $a=13.0204(6)$ Å, $b=6.19.54(3)$ Å, $c=26.6900(11)$ Å, $\alpha=\gamma=90°$, $\beta=92.167(3)°$, $V=2151.45(17)$ $Å^3$, $Z=8$, $D_{cal}=1.16$ g cm^{-3}, $\mu=0.08$ mm^{-1}, $F(OOO)=832$. Data were collected on a crystal of size $0.30\times0.05\times0.02$ mm^3 on a KappaCCD diffractometer operating for $4.54<\theta<25.5°$. Reflections of 21,352 were collected for $-15\le h\le15$, $-7\le k\le7$, $-31\le l\le31$. There were 3794 independent reflections with 2489 possessing $I>2\sigma(I)$. The structure was refined using SHELXL-97 by full matrix least-squares on F^2. The goodness-of-fit on F^2 was 1.027. The final *R* indices were $[I>2\sigma(I)]$ $R_1=0.06$, $wR_2=0.137$ and the *R* indices (all data) were $R_1=0.101$ and $wR_2=0.156$. The largest difference peak and hole were 0.22 and -0.25 e $Å^{-3}$.

4.2.2. *cis*-1,2-Dihydroxy-*trans*-3-methoxy-1,5,5-trimethylcyclohexane (7). $C_{10}H_{20}O_3$, M_r 188.26, triclinic, $P\bar{1}$ (no. 2), $a=6.0870$ (4) Å, $b=8.2022(5)$ Å, $c=10.9679(6)$ Å, $\alpha=93.845(4)°$, $\beta=93.766(4)°$, $\gamma=96.477(4)°$, $V=541.39(6)$ $Å^3$, $Z=2$, $D_{cal}=1.16$ g cm^{-3}, $\mu=0.08$ mm^{-1}, $F(OOO)=208$. Data were collected on a crystal of size $0.2\times0.1\times0.1$ mm^3 on a KappaCCD diffractometer operating for $4.64<\theta<25.08°$. 4993 Reflections were collected for $-7\le h\le5$, $-9\le k\le9$, $-13\le l\le13$. There were 1900 independent reflections with 1574 possessing $I>2\sigma(I)$. The structure was refined using SHELXL-97 by full matrix least-squares on F^2. The

goodness-of-fit on F^2 was 1.088. The final R indices were $[I>2\sigma(I)]$ $R_1=0.04$, $wR_2=0.098$ and the R indices (all data) were $R_1=0.051$ and $wR_2=0.105$. The largest difference peak and hole were 0.19 and -0.21 e Å^{-3}.

4.2.3. 2α,8-Dihydroxy-1β-methoxy-*p*-menthane (13). $C_{11}H_{22}O_3$, M_r 202.29, orthorhombic, space group *Pbca* (no. 61), $a=8.0065(2)$ Å, $b=14.5231(4)$ Å, $c=19.9634(7)$ Å, $\alpha=\beta=\gamma=90°$, $V=2321.33(12)$ Å^3, $Z=8$, $D_{cal}=1.16$ mg cm^{-3}, $\mu=0.08$ mm^{-1}, $F(OOO)=896$. Data were collected on a crystal of size $0.50\times0.20\times0.10$ mm^3 on a KappaCCD diffractometer operating for $3.92<\theta<25.3°$. Reflections of 10,732 were collected for $-9\le h\le 19$, $-15\le k\le 14$, $-17\le l\le 21$. There were 1878 independent reflections with 1556 possessing $I>2\sigma(I)$. The structure was refined using SHELXL-97 by full matrix least-squares on F^2. The goodness-of-fit on F^2 was 1.068. The final R indices were $[I>2\sigma(I)]$ $R_1=0.060$, $wR_2=0.151$ and the R indices (all data) were $R_1=0.073$ and $wR_2=0.161$. The largest difference peak and hole were 0.37 and -0.26 e Å^{-3}.

5. Crystallographic data

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 247473, 247474, 247475. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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Corrigendum

Corrigendum to "Enantioselective alkylation and protonation of prochiral enolates in the asymmetric synthesis of β-amino acids" [Tetrahedron 59 (2003) 4223]

Roberto Melgar-Fernández, Rodrigo González-Olvera and Eusebio Juaristi*

Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apartado Postal 14-740, 07000 México, D.F., Mexico

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Abstract—This paper describes work that corrects the synthetic procedures reported in the title paper for the preparation of novel chiral phenolic acids (*S*)-**11**, (*S*)-**13**, (*S*,*S*)-**12** and (*S*,*S*)-**14**. Unlike the results provided in the article being reexamined, protonation of prochiral enolates **2**-Li and **3**-Li with chiral Brønsted acids **11**–**14** proceeded with negligible enantioselectivity.

A central section in the above manuscript describes the enantioselective protonation of prochiral enolates **2**-Li and **3**-Li with novel chiral phenolic acids (*S*)-**11**, (*S*)-**13**, (*S*,*S*)-**12** and (*S*,*S*)-**14** (Chart 1).

While novel chiral amide (*S*)-**11** is readily prepared by treatment of 3*H*-benzofuran-2-one with α-phenylethylamine under mild conditions (Scheme 1a), we were unable to reproduce the described procedure for the preparation of 2-(2-hydroxyphenyl)-*N*,*N*-bis-(1*S*-α-phenylethyl)acetamide, (*S*,*S*)-**12**, by refluxing 3*H*-benzofuran-2-one and (*S*,*S*)-bis-α-phenylethylamine in toluene (Scheme 1b). In our hands, reaction did not proceed even in the presence of strong Lewis acids such as diethylaluminum chloride, sealed ampule, or under microwave irradiation.

We have now developed a successful route for the synthesis of chiral phenol (*S*,*S*)-**12**, which uses (2-hydroxyphenyl)-acetic acid **15** as starting material (Scheme 2).

Regarding the protonation reaction of enolates **2**-Li and **3**-Li with chiral Brønsted acids **11**–**14**, contrary to the information provided in Table 4 of the article being reexamined, we found no enantiomeric excess in the recovered pyrimidinones **2** and **3**.[1,2]

Figures 1 and 2 show the molecular structure and solid state conformation of *O*-benzyl precursor (*S*,*S*)-**17** and the desired chiral amide (*S*,*S*)-**12**, respectively.

In this corrigendum, we also provide revised procedures and analytical data for aminophenols (*S*)-**13** and (*S*,*S*)-**14**, which were prepared by lithium aluminum hydride reduction of amides (*S*)-**11** and (*S*,*S*)-**12**, respectively (Scheme 3).

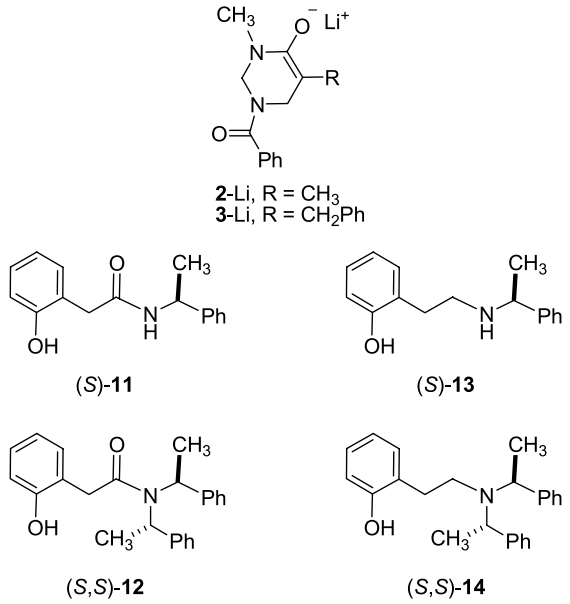

Chart 1.

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Keywords: Chiral ligands; Chiral Brønsted acids; Enantioselective protonations; Amino acids and derivatives.
* Corresponding author. Tel.: +52 55 5061 3722; fax: +52 55 5747 7132; e-mail: juaristi@relaq.mx

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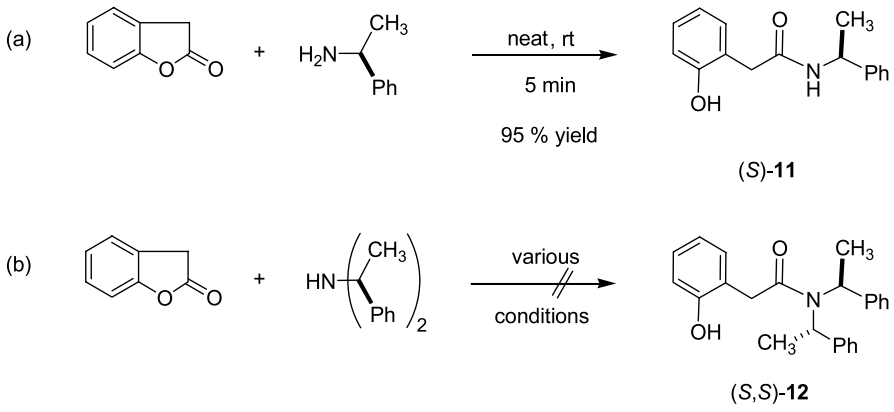
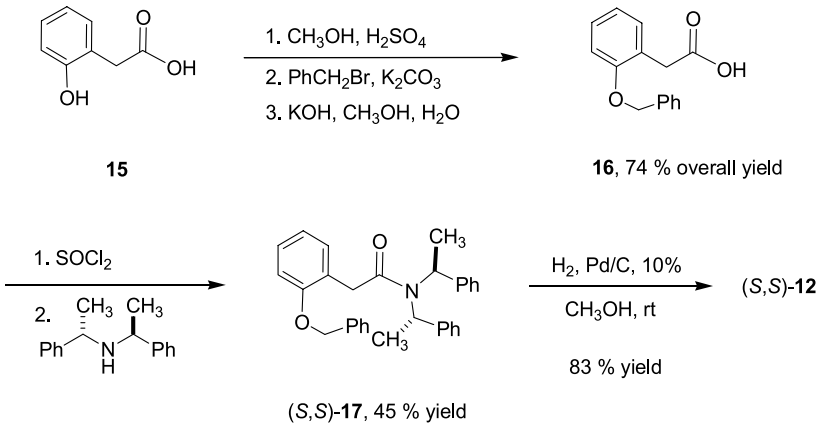


Scheme 1.



Scheme 2.

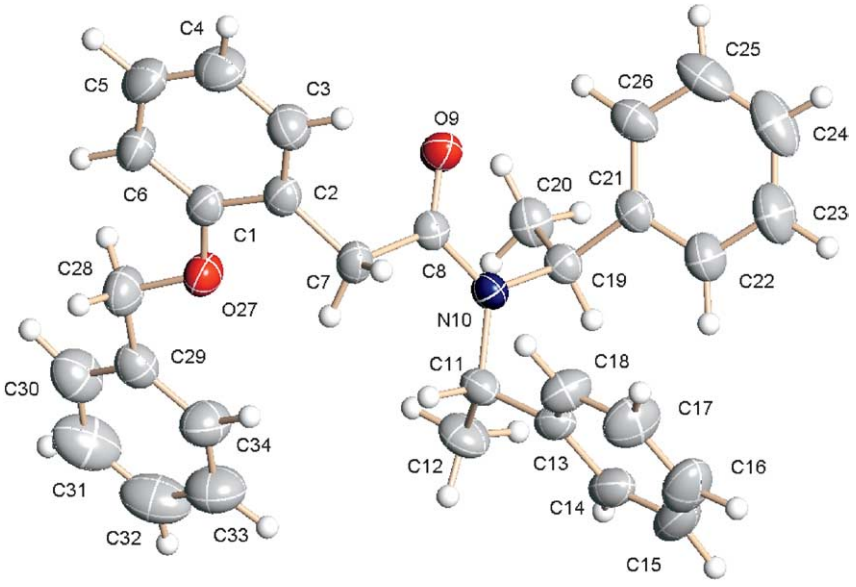


Figure 1. X-ray crystallographic structure and solid-state conformation of (*S*,*S*)-**17**.[3]

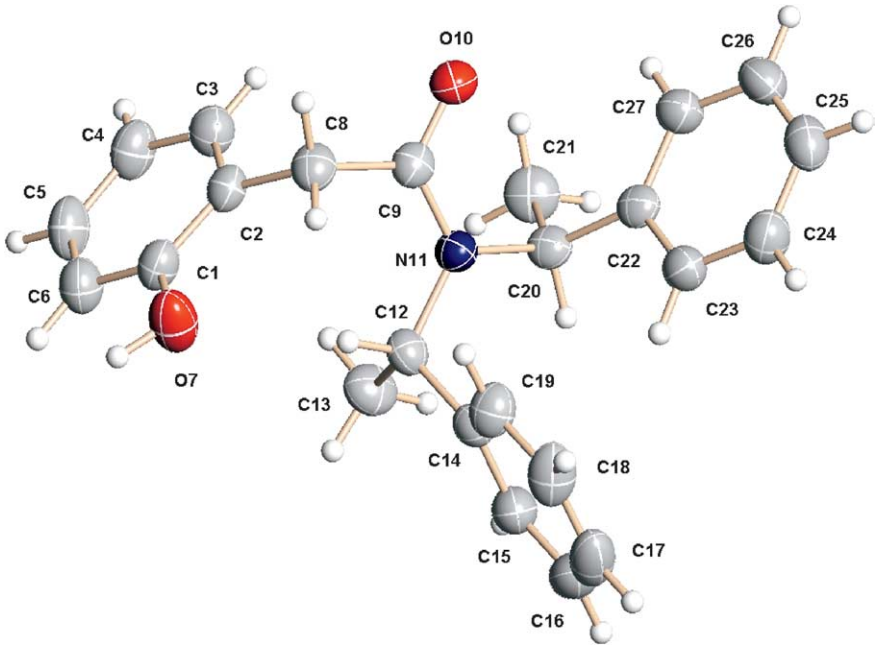
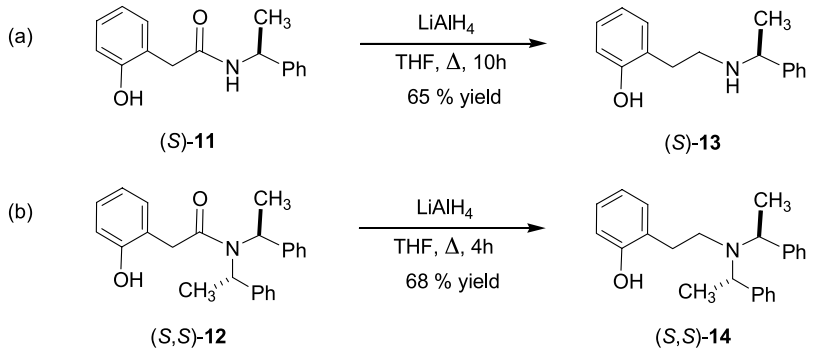


Figure 2. X-ray crystallographic structure and solid-state conformation of (*S*,*S*)-**12**.[3]



Scheme 3.

1. Experimental

1.1. Spectral data for compounds

1.1.1. 2-(2-Hydroxyphenyl)-*N*-(1*S*-α-phenylethyl)acetamide, (*S*)-11. In a 100 mL round-bottom flask was placed 1.5 g (11.2 mmol) of 3*H*-benzofuran-2-one and 1.35 g (11.2 mmol) of (*S*)-α-phenylethylamine, and the resulting mixture was stirred for 5 min at ambient temperature. A 9:1 mixture of hexane and toluene (50 mL) was added and stirring was continued for 30 min at ambient temperature. The precipitated product was filtered and dried to furnish 2.7 g (95% yield) of (*S*)-**11** as a slightly yellowish solid, mp 118–119 °C, $[\alpha]_D^{20} = -72.2$ ($c = 1.0$, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 1.45 (d, $J = 6.9$ Hz, 3H), 3.55 (dd, $J^1 = 14.3$ Hz, $J^2 = 4.1$ Hz, 2H), 5.06 (dq, $J^1 \cong J^2 = 7.3$ Hz, 1H), 6.56 (d, $J = 6.9$ Hz, 1H), 6.80–7.32 (m, 9H), 9.87 (s, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 21.7, 41.1, 49.7, 118.0, 120.5, 121.7, 126.2, 127.7, 128.9, 129.3, 130.7, 142.4, 156.1, 172.7. IR (KBr) ν (cm^{-1}): 3317, 1620, 1546, 1456, 1265, 1234. MS *m*/*z* (%): 255 (M^+, 59), 151 (42), 134 (40), 105 (100), 79 (8). Anal. Calcd for $C_{16}H_{17}NO_2$ (255.32): C, 75.27; H, 6.71; N, 5.49. Found: C, 75.05; H, 6.74; N, 5.85.

1.1.2. 2-[2-(1*S*-α-Phenylethylamino)ethyl]phenol, (*S*)-13. In a 100 mL round-bottom flask was placed 0.74 g (19.5 mmol) of $LiAlH_4$ and 30 mL of anhyd THF. The resulting suspension was treated with 1.0 g (3.9 mmol) of (*S*)-**11** and heated to reflux for 10 h. Quenching was effected with $Na_2SO_4 \cdot 10H_2O$, and the resulting mixture was filtered over Celite. The filtrate was concentrated and distilled at reduced pressure to afford 0.6 g (65% yield) of (*S*)-**13** as a slightly yellowish oil, bp 140 °C/0.5 mmHg. $[\alpha]_D^{20} = +13.2$ ($c = 1.0$, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 1.41 (d, $J =$ 6.9 Hz, 3H), 2.67–2.80 (m, 4H), 3.78 (q, $J = 6.9$ Hz, 1H), 6.68–6.74 (m, 1H), 6.89–6.94 (m, 2H), 7.07–7.13 (m, 1H), 7.20–7.34 (m, 5H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 23.1, 34.6, 47.9, 58.3, 117.7, 119.2, 126.7, 127.7, 127.8, 128.3, 129.0, 131.1, 157.2. IR (neat) ν (cm^{-1}): 3278, 2934, 2572, 1581, 1485, 1262, 1107, 757. MS *m*/*z* (%): 241 (5), 134 (51),

105 (100), 77 (20). HRMS: (FAB) *m/z* calcd for $C_{16}H_{20}NO$ $(M + H)^+$ 242.1545, found 242.1550.

1.1.3. 2-[2-(Benzyloxy)phenyl)]acetic acid, 16. According to the procedures described in the literature,[4–6] (2-hydroxyphenyl)acetic acid **15** (5.0 g, 32.9 mmol) was suspended in methanol (50 mL) and treated with 1.0 mL of concd sulfuric acid to give 5.4 g (99% yield) of the expected ester, methyl 2-(2-hydroxyphenyl)acetate, mp 66–68 °C (lit.[4] mp 64 °C). *O*-Benzylation of this product (2.5 g, 15.0 mmol) was achieved with benzyl bromide (1.8 mL, 15.0 mmol) and K_2CO_3 (2.5 g, 18.0 mmol) to give 3.2 g (85% yield) of methyl 2-[2-(benzyloxy)phenyl]acetate as a colourless liquid, bp 143 °C/0.5 mmHg (lit.[5] bp 155–160 °C/0.3 mmHg). Saponification of this product (3.0 g, 11.7 mmol) was accomplished with KOH (1.7 g, 23.5 mmol) in methanolic solution. The crude product was crystallized from hexane to afford 2.5 g, (88% yield) of **16** as a white solid, mp 91–93 °C (lit.[6] mp 94 °C). ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.76 (s, 2H), 5.10 (s, 2H), 6.90–7.00 (m, 2H), 7.25–7.50 (m, 7H), 10.76 (bs, 1H). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 36.2, 70.1, 112.0, 121.0, 122.9, 127.2, 128.0, 128.7, 129.0, 131.3, 137.0, 156.7, 178.6. IR (KBr) ν (cm^{-1}): 3029, 2921, 1708, 1602, 1492, 1228, 733.

1.1.4. 2-[2-(Benzyloxy)phenyl]-*N*,*N*-bis(1*S*-α-phenylethyl)acetamide, (*S*,*S*)-17. In a 250 mL round-bottom flask was placed 1.3 g (5.36 mmol) of **16** and 10 mL of dry toluene. The resulting solution was treated with 1.3 g (11.0 mmol) of $SOCl_2$ and heated to 50 °C for 1 h. Excess thionyl chloride was removed under vacuum and the residue was suspended in 20 mL of dry toluene to be added dropwise (via cannula) at −60 °C to a solution of (*S*,*S*)-bis-α-phenylethylamine dissolved in 50 mL of dry toluene. The reaction mixture was allowed to warm up to ambient temperature and stirring was continued at this temperature for 15 h. The toluene was removed in a rotary evaporator and the residue was resuspended in EtOAc, washed with water, dried over anhyd Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography (CH_2Cl_2-hexane, 9:1) and crystallized from hexane to give 1.1 g (45% yield) of (*S*,*S*)-**17** as white solid, mp 106–107 °C. $[\alpha]_D^{20} = -88.4$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.59 (d, $J = 5.8$ Hz, 3H), 1.77 (d, $J = 5.8$ Hz, 3H), 3.54 (d, $J = 15.8$ Hz, 1H), 3.82 (d, $J = 15.8$ Hz, 1H), 5.08 (s, 2H), 5.15 (b, 2H), 6.97–7.31 (m, 14H), 7.40 (s, 5H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 18.2, 37.1, 52.9, 53.8, 70.0 111.6, 120.8, 124.7, 126.7, 127.6, 127.6, 127.8, 128.0, 128.2, 128.4, 130.7, 136.9, 140.6, 141.4, 155.9, 171.0. IR (KBr) ν (cm^{-1}): 3029, 2973, 1651, 1602, 1496, 1433, 1263, 1026, 750, 695. MS *m/z* (%): 450 (M^+, 3), 344 (100), 210 (73), 120 (52), 105 (93), 91 (90). X-ray crystallographic structure, see Figure 1. Anal. Calcd for $C_{31}H_{31}NO_2$: C, 82.82; H, 6.95; N, 3.12. Found: C, 82.59; H, 6.76; N, 3.48.

1.1.5. 2-(2-Hydroxyphenyl)-*N*,*N*-bis(1*S*-α-phenylethyl)-acetamide, (*S*,*S*)-12. In a 250 mL hydrogenation flask was placed 0.9 g (2.0 mmol) of (*S*,*S*)-**17**, 0.09 g of 10% Pd/C, and 50 mL of methanol. The flask was pressurized to 65 psi of H_2 and stirred at ambient temperature for 8 h. The catalyst was removed by filtration and the filtrate was concentrated at reduced pressure. The crude product was purified by column chromatography (CH_2Cl_2–hexane, 9:1) and crystallized from hexane to give 0.59 g (83% yield) of (*S*,*S*)-**12**, as a white solid, mp 119–120 °C. $[\alpha]_D^{20} = -184.1$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.73 (d, $J = 7.3$ Hz, 3H), 1.92 (d, $J = 7.0$ Hz, 3H), 3.39 (d, $J = 14.5$ Hz, 1H), 3.55 (d, $J = 14.5$ Hz, 1H), 4.97 (q, $J = 6.9$ Hz, 1H), 5.94 (bs, 1H), 6.10 (bs, 1H), 6.60 (t, $J = 7.3$ Hz, 1H), 6.85–6.97 (m, 3H), 7.12 (dt, $J^1 = 8.1$ Hz, $J^2 = 1.4$ Hz, 1H), 7.18–7.40 (m, 9H), 10.8 (s, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 17.9, 20.9, 39.9, 52.5, 53.5, 118.5, 119.8, 121.9, 126.6, 127.9, 128.5, 128.8, 129.0, 129.2, 129.3, 131.0, 140.1, 141.5, 157.6, 175.3. IR (KBr) ν (cm^{-1}): 3086, 1616, 1589, 1455, 1336, 1168. MS *m/z* (%): 359 (M^+, 5), 255 (100), 210 (19), 105 (97), 91 (13). X-ray crystallographic structure, see Figure 2. Anal. Calcd for $C_{24}H_{25}NO_2$ (359.47): C, 80.19; H, 7.01; N, 3.90. Found: C, 79.84; H, 7.35; N, 3.98.

1.1.6. 2-{[2-bis(1*S*-α-Phenylethyl)amino]ethyl}phenol, (*S*,*S*)-14. In a 100 mL round-button flask was placed 0.12 g (3.2 mmol) of $LiAlH_4$ and 30 mL anhyd THF. To the resulting suspension was added 0.23 g (0.64 mmol) of (*S*,*S*)-**12** and the resulting mixture was heated to reflux for 4 h. Quenching was effected with $Na_2SO_4 \cdot 10H_2O$ (CAUTION: evolution of H_2). Filtration over Celite and concentration of the filtrate afforded the crude product, that was purified by column chromatography (hexane–EtOAc, 9:1) and crystallized from hexane to give 0.15 g (68% yield) of (*S*,*S*)-**14** as a white solid, mp 86–88 °C. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.35 (d, $J = 6.9$ Hz, 6H), 2.56–2.69 (m, 2H), 3.09–3.19 (m, 1H), 3.24–3.36 (m, 1H), 3.86 (q, $J = 6.9$ Hz, 2H), 6.76–6.82 (m, 1H), 6.92–7.02 (m, 2H), 7.11–7.17 (m, 1H), 7.22–7.37 (m, 10H), 11.93 (bs, 1H). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 21.6, 35.5, 49.7, 61.4, 117.4, 119.7, 127.4, 128.3, 128.6, 128.8, 130.4, 142.0, 156.9. IR (KBr) ν (cm^{-1}): 3446, 2976, 2597, 1584, 1489, 1263, 1089, 756. MS *m/z* (%): 346 ($M^+ + 1$, 21), 345 (M^+, 7), 238 (100), 134 (80), 105 (100), 91 (42), 79 (67). Anal. Calcd for $C_{24}H_{27}NO$ (345.48): C, 83.44; H, 7.88; N, 4.05. Found: C, 83.00; H, 8.18; N, 3.88.

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References and notes

1. Both the protonation procedure described in the article being reexamined and the general protocol developed by Fehr et al. [Fehr, C.; Galindo, J.; Farris, I.; Cuenca, A. *Helv. Chim. Acta*, **2004**, *87*, 1737] were followed.
2. HPLC analysis using a Chiralcel OD column (for **2**) and a Chiralcel OJ column (for **3**). Hexane–isopropanol, 90:10. 210 nm UV detector, 1.0 mL/min.
3. Crystal data for (*S*,*S*)-**12**: Orthorhombic $P2_12_12_1$, $a = 6.5233(3)$ Å, $b = 15.3296(7)$ Å, $c = 20.6603(12)$ Å, $\alpha = 90.0°$,

$\beta=90.0°$, $\gamma=90.0°$, $V=2066.02(18)$ Å^3, $R_1=0.0504$ ($wR_2=0.0937$); for (*S*,*S*)-**17**: Monoclinic $P2_1$, $a=11.9153(2)$ Å, $b=7.8766(2)$ Å, $c=13.6590(3)$ Å, $\alpha=90.0°$, $\beta=103.8080(10)°$, $\gamma=90.0°$, $V=1244.88(5)$ Å^3, $R_1=0.0395$ ($wR_2=0.0791$). Atomic coordinates for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 IEZ, UK. (Fax: +44 1223 336 036. e-mail: deposit@ccdc.cam.ac.uk; Deposition number: CCDC 256121, CCDC 256122.

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