The Efficiency of the Metal Catalysts in the Nucleophilic Substitution of Alcohols is Dependent on the Nucleophile and Not on the Electrophile

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Abstract: In this study, we investigate the effect of the electrophiles and the nucleophiles for eight catalysts in the catalytic $S_N 1$ type substitution of alcohols with different degree of activation by sulfur-, carbon-, oxygen-, and nitrogen-centered nucleophiles. The catalysts do not show any general variance in efficiency or selectivity with respect to the alcohols and follow the trend of alcohol reactivity. However, when it comes to the nucleophile, the eight catalysts show general and specific variances in the efficiency and selectivity to perform the desired substitution. Interestingly, the selectivity of the alcohols to produce the desired substitution products was found to be independent of the electrophilicity of the generated carbocations but highly dependent on the ease of formation of the cation. Catalysts based on iron(III), bismuth-(III), and gold(III) show higher conver-

Keywords: alcohols • atom economy • homogeneous catalysis • nucleophilic substitution sions for S-, C-, and N-centered nucleophiles, and Bi^{III} was the most efficient catalyst in all combinations. Catalysts based on rhenium(I) or rhenium(VII), palladium(II), and lanthanum(III) were the most efficient in performing the nucleophilic substitution on the various alcohols with the O-centered nucleophiles. These catalysts generate the symmetrical ether as a by-product from the reactions of S-, C-, and N-centered nucleophiles as well, resulting in lower chemoselectivity.

FULL PAPER

Introduction

Activation of the hydroxy group is fundamental to organic chemistry when alcohols are used as substrates in nucleophilic substitutions. Traditionally, the hydroxy group is converted into a better leaving group in a separate step (Scheme 1). The conversion of the hydroxy group into, for

$$R \frown OH \xrightarrow{\text{TsCI, base}} R \frown OTs \xrightarrow{\text{Nu-H}} R \frown Nu$$

Scheme 1. Traditional substitution of the hydroxy group requires an additional step, uses a stoichiometric amount of reagents, and generates waste.

example, a tosyl group or a halide, requires the addition of stoichiometric amounts of reagent and base and also makes the synthetic procedure one step longer.^[1] The intermediates that form are often carcinogenic due to their strong alkylating properties. Furthermore, stoichiometric amounts waste is generated in the subsequent nucleophilic substitution step. An alternative route, used for stereospecific substitutions of enantioenriched alcohols, is the one-step Mitsunobu reac-

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metric amounts of waste, which gives rise to tedious purification problems. From perspectives of safety, environment, and economy, these stoichiometric and waste-generating methodologies are not desirable.^[4] This fact was recently acknowledged when the nucleophilic substitution of alcohols was selected as the second most desired reaction that pharmaceutical companies wanted greener alternatives for.^[5] Catalytic nucleophilic substitution of alcohols is an attrac-

Catalytic nucleophilic substitution of alcohols is an attractive and useful synthetic tool, which owes its efficiency to the atoms and heeds environmental constraints, since water is the only by-product of this single-step reaction (Scheme 2).^[6] Various metal complexes have been reported

tion.^[2] However, this reaction requires stoichiometric carncinogenic and explosive DEAD^[3] and also generates stoichio-

$$R^{1} OH + Nu-H \longrightarrow R^{1} Nu + H_{2}O$$

Scheme 2. Catalytic nucleophilic substitution of alcohols. [M]=metal-based catalyst.

to be active for the catalytic nucleophilic substitution of alcohols. Lewis acids based on metal salts, such as iron(III),^[7] bismuth(III),^[8] boron(III),^[9] cerium(III),^[10] indium(III),^[11] gold(III),^[12] rhenium(V),^[13] rhenium(VII),^[14] and lanthanum(III),^[15] have been reported to catalyze nucleophilic substitution of different alcohols. Also, certain transition metals prone to cycle between different oxidation states, such as ruthenium(I,II),^[16] rhenium(I,III),^[17] iridium-(I,III),^[18] and palladium(0,II),^[19] have been reported to be active for this transformation.

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The research field of catalytic nucleophilic substitution of alcohols is difficult to overview. To our knowledge, there is only one review that covers the research topic.^[20] The greatest challenge to the understanding of the reactivity is that different research groups use different reaction conditions. Table 1 gives an example of an etherification reaction be-

Table 1. Representative reports on the catalyzed etherification reaction in the literature.

	Ar OH + I	R-OH —	`	Ar C	^R +	H ₂ O	
Entry ^{[ref}	Catalyst	Catalyst loading [mol %]	Т [°С]	Solvent	ROH [equiv]	<i>t</i> [h]	Conv. [%]
1 ^[12a]	NaAuCl ₄	2	70	_	5	1	58
2[17]	[ReBr(CO)] ₅	3	160	-	5	12	87
3 ^[14]	ReMeO ₃	2	rt	C_6H_6	10	48	91
4 ^[7a]	FeCl ₃	20	40	-	150	n.r. ^[b]	0
5 ^[19a]	[PdCl ₂ (diop)] ^[a]	4	50	$MeNO_2$	1	24	99

[a] diop=4*R*,5*R*-(+)-*O*-Isopropylidene-2,3-di-hydroxy-1,4-bis(diphenylphosphanyl)butane. [b] Not reported.

tween a primary aliphatic alcohol (nucleophile) and a primary benzylic alcohol (electrophile). The following issues make a comparison between the catalysts impossible: 1) catalyst loadings vary between 2 and 20 mol %, 2) reaction temperatures vary between room temperature and 160 °C, 3) some reports use solvent where others do not, 4) the nucleophile is used in either an equimolar amount or in excess, 5) reaction time varies from 1 to 48 h. To our knowledge, there are no attempts to evaluate the performance of the different catalysts with respect to electrophile or nucleophile.

Herein, we study the scope and limitations of nucleophilic substitution of alcohols with respect to the catalyst and the electrophile as well as the nucleophile. We investigate whether certain metal catalysts have 1) higher rates of conversion for certain electrophiles, 2) higher regioselectivity in allylic and propargylic alcohols, 3) higher rates of conversion for certain nucleophiles, 4) higher chemoselectivity for certain nucleophiles. To our knowledge, this is the first comprehensive study on the catalytic nucleophilic substitution of alcohols that covers a broad range of both electrophiles and nucleophiles.

Results and Discussion

In order to perform a comprehensive study of the catalytic nucleophilic substitution of alcohols, the choices of electrophiles, nucleophiles, and metal catalysts are pivotal. In this section, a discussion regarding the choices made for this study will be presented.

Choice of Electrophiles

We have chosen five different alcohols, all of which have different degrees of activation (Scheme 3). The aim was to map the reactivity of 1) alcohols with different degrees of activation and 2) different activating groups (benzyl, allyl, propargyl, alkyl). Another aim was to use substrates that may react at different positions and thereby map regioselectivity in, for example, allyl and propargyl alcohols.



Scheme 3. Alcohols used in the current study. PMP=para-methoxyphen-yl.

In a precise and well-defined study, an electrophilicity parameter and two nucleophilicity parameters have been introduced by Mayr et al.^[21] in describing the rate of reaction between a carbocationic electrophile and a nucleophile.^[21a] The most important outcome of their study is to consider all the parameters, such as electrophilicity of the generated carbocation, nucleophilic properties of the nucleophile, as well as the solvent and the generated by-product while defining an empirical scale of reactivity applicable for S_N1 type reactions.^[21b] Moreover, they have established a rule explaining the feasibility of the reaction between a given electrophile–nucleophile pair.^[21c]

Interestingly, in the present study, the efficiency order of the electrophilic alcohols in terms of selectivity to form the desired substitution products was found to be governed by the ease of generating the corresponding carbocation rather than the electrophilicity of the generated cation.

4-Methoxybenzyl alcohol (1a) was the most efficient alcohol to generate the desired products in this study. The second next reactive alcohol, 4-phenyl-3-butene-2-ol (1b) was chosen in order to discriminate the allylic reactivity.^[7i] It was chosen over the far more commonly used 1,3-diphenyl-2-propen-1-ol,^[11a,16g] which does not discriminate between benzylic and allylic reactivity. 1-Phenylethanol (1c) is a frequently used substrate in catalytic nucleophilic substitution studies and was chosen to represent a secondary benzylic alcohol with medium reactivity.^[7c,11a] tert-Butyl alcohol (1d) was chosen to represent a tertiary alkyl alcohol.^[12a] tert-Butyl alcohol was found to be susceptible to water elimination, producing volatile isobutylene in appreciable amount in case of most of the catalyst where no or low amount of product formation was observed (see the Supporting Information for details).^[8b] 4-Phenyl-3-butyn-2-ol (1e) was chosen over the more frequently used 1,3-diphenyl^[7n,8d] analogue for the same reason as for the allylic substrate (see above). For both substrates 1b and 1e, the attack on the nu**CHEMISTRY**

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cleophile could occur at either the benzylic or alcoholic positions and therefore, these substrates may discriminate regioselectivity.

Choice of Nucleophiles

We have chosen four different nucleophiles, with different atom centers (S, C, O, N) to distinguish between the compatibility of the nucleophile and that of the catalyst (Scheme 4). Another aim was to determine the efficiency of the metal catalysts with hard–soft (O-, S-centered) nucleophiles as compared to their efficiency with weak–strong (amide, thiol) nucleophiles.



Scheme 4. Nucleophiles used in the current study.

The commonly used thiophenol (2a) was chosen to represent a soft and strong nucleophile in this study. Acetyl acetone (2b) was chosen to represent a strong and soft nucleophile in which the enolate formation may be promoted by Lewis acids.^[7c,o] We chose 3-phenyl propanol $(2c)^{[12a]}$ as an O-centered nucleophile because this substrate is not volatile and can easily be monitored by TLC. Attempts to employ phenol as an O-centered nucleophile were unsuccessful in a pre-screening, probably because of the strong complex formation between the phenolic OH group and the metal, which would deactivate the catalyst. Benzamide (2d), the weakest nucleophile, was chosen because aniline was observed to generate a complex with certain metals and *para*toluenesulfonamide was not reactive with some of the alcohols in an initial screening.

Choice of Catalysts

In a preliminary study, we included 20 catalysts that were found in the literature of related studies.^[7–19] However, the study became too extensive to provide an accessible overview, and some of the catalysts showed similar reactivity. For example, the anion effect was studied for BiBr₃, BiCl₃, and BiI₃, and only a negligible difference in efficiency was observed. Therefore, after an initial screening, eight catalysts were selected (Scheme 5). These catalysts have all been reported in one or more of the different combinations of electrophiles and nucleophiles. We have divided the catalysts into three different categories: Lewis acidic metals, redox metals, and mineral acids.

 $\label{eq:FeCl_3} \begin{array}{lll} FeCl_3 & BiBr_3 & NaAuCl_4\cdot 2H_2O & La(OTf)_3 \\ \\ \left[PdCl_2(MeCN)_2\right] & \left[ReBr(CO)_5\right] & MeReO_3 & HCl \\ \\ Scheme 5. Catalysts used in the current study. \end{array}$

Lewis Acidic Metals

To study how the hardness or softness and the group identity (main group, transition metal, lanthanide) of the metal influence the efficiency to perform the reaction with respect to both the electrophile and the nucleophile, different Lewis acids (iron(III) chloride, bismuth(III) bromide, sodium tetrachloroaurate(III) dehydrate and lanthanum(III) triflate) were selected. Fe^{III} has been reported to be active in C–O,^[7a,b,f] C–N,^[7k,m,n] and C–C bond-forming reactions^[7c] with benzyl alcohols. Bi^{III} has been reported to be active in various reactions, including C–C,^[8a,b,c] C–O,^[8d] C–S,^[8f] and C–N^[8e] bond-forming reactions. Au^{III} has been reported to be active in etherification^[12a] and amidation^[12b,c] of benzylic and tertiary alkyl alcohols. Lanthanoid salts have been reported to be active in C–C, C–O, and C–N bond-forming reactions but not in C–S bond-forming reactions.^[15]

Redox Metals

We wanted to compare how the oxidation state of the transition metal affected the compatibility with the nucleophile as well as the electrophile. Also, we wanted to study how different transition metals that have been reported to be active for different activating groups (i.e. Pd to allyls and Re to alkynes) perform on the selected substrates. Bis(acetonitrile)palladium(II)chloride, bromorhenium(I)pentacarbonyl and methylrhenium(VII)trioxide represent the redox metal catalysts in this study. Pd^{II} has been reported to be active in C-O, C-N, and C-S bond-forming reactions and is prone to form π -allyl complexes with allylic alcohols.^[19a,b] The Re^I carbonyl compound has been reported to be active in C-O bond-forming reactions and is reported to form π -propargyl complexes with propargylic alcohols.^[14] Re^{VII} does not have the possibility to perform oxidative addition and has been reported to be active in C-O and C-N bond-forming reactions. It should be pointed out in this respect that Au^{III} can also act as a redox-metal catalyst (Au^{III}/Au^I).

Mineral Acids

We chose HCl as our mineral acid, because the Lewis acids in our study may act as a precursor to generate the corresponding mineral acid that could be the true catalyst.^[8e] To achieve adequate comparison, 20 mol% instead of 5 mol% has been used with respect to the corresponding electrophilic alcohol.

Catalytic Procedure

Reference compounds of all products were prepared using catalytic methods in which the alcohol and nucleophile reacted in the presence of an appropriate catalyst. In many reactions, side reactions, such as homo-etherification to generate the symmetrical ether were observed. All by-products were isolated and characterized separately. Temperatures and reaction times of all reactions were pre-screened. It is important to note that these reaction parameters were set in order to differentiate between the reactivity of the combinations in transformations. That is, the reaction parameters

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were not optimized to generate the corresponding products in high yields, but to disclose differences in reactivity among the electrophiles, nucleophiles and catalysts.

Choice of Solvent

Pre-screening revealed nitromethane to be the best solvent for all nucleophile–electrophile combinations. Dichloroethane showed similar reactivity for reactions that were efficient at low temperature. However, certain combinations of electrophile and nucleophile required higher reaction temperature. Running the reactions in toluene gave poor results.

Catalytic Nucleophilic Substitution by S-Centered Nucleophile **2** *a*

The results from the thioetherification reactions are given in Table 2. The reactions were run under three different reaction conditions, depending on the electrophile. Reactions employing substrates **1a–1c** were run at room temperature for 10 h, **1e** was run at 60 °C for 60 h, and **1d** was run at 80 °C for 48 h. It is worth noting that, of the metals screened in this study, only La^{III}, Bi^{III}, and Pd^{II} have been reported to be active in the thioetherification reaction before.^[15,19a]

of substrate **1b**. If the reaction proceeded through a π -allyl intermediate, such regioisomers would be expected.

For the less reactive alcohols (1d, e) in terms of selectivity towards formation of the desired substitution product, the Lewis acids promoted the thioetherification better, while the redox metals showed low or no conversion to the desired product. Bi^{III} showed the highest degree of efficiency and generated the desired products in a 50-79% yield. Re^I catalysts, which are known to generate π -propargylic metal complexes, were unreactive in this transformation.^[22] In analogy to substrates 1a-c, etherification of 1e to generate the symmetrical ether was observed. Using Bi^{III} or Fe^{III} catalysts, symmetrical ethers were obtained in a 23-26% yield. In the case of Au^{III}, an attack of the triple bond of **1e** was observed.^[23] Moreover, the reactions involving tert-butyl alcohol 1d produced isobutylene as the major side product for all the catalyst except bismuth, which generated 3d in 79% yield (see the Supporting Information for details). The catalysts that gave low conversion in direct substitution reactions leading to thioetherification generally ended up with more disulfide formation by oxidation of the unreacted thiophenol.

Table 2. Conversion in the catalytic nucleophilic substitution of alcohols (1) by thiophenol (2a).^[a,b]

	OH R ¹ R ² 1a-e	+ Ph-SH <u>5 mol</u> Me	[™] [M] S ^F NO ₂ R ¹ F 3a-e	^p h + H ₂ O 1 ²	
Products	PMP [^] SPh 3a	SPh Ph 3b	SPh Ph 3c	Ph	PhS
Catalysts					
FeCl ₃	69 %	59%	88 %	47 % (70 %) ^[c,d]	trace (82%) ^[e]
BiBr ₃	92 %	86 %	99 %	50 % (85 %) ^[c]	79 %
NaAuCl ₄ ·2H ₂ O	81 %	66% (78%) ^[c]	41 % (61 %) ^[c]	16% ^[d]	$12\% (45\%)^{[e]}$
La(OTf) ₃	66 % (79 %) ^[c]	74 %	$10\% (23\%)^{[c]}$	$10\% (30\%)^{[c]}$	30 % (89 %) ^[c,e]
[PdCl ₂ (MeCN) ₂]	$62\% (73\%)^{[c]}$	61 %	38% (57%) ^[c]	0% ^[d]	$0\% (21\%)^{[e]}$
[ReBr(CO) ₅]	0%	50 % ^[d]	0 % ^[d]	0 % ^[d]	13 % (57 %) ^[e]
MeReO ₃	80 %	61% (71%) ^[c,d]	$48\% (78\%)^{[c,d]}$	19% ^[d]	$6\% (51\%)^{[e]}$
HCl ^[f]	79%	53 % ^[c]	32% (54%) ^[c]	$8\%^{[d]}$	0% (23%) ^[e]

[a] The reactions were run using alcohol 1 (1 mmol), 2a (1 mmol) in nitromethane (2.5 mL), and metal catalyst (5 mol%). Reactions to form 3a-c were run at room temperature for 10 h. The reaction to form 3e was run at 60 °C for 60 h. The reaction to form 3d was run at 80 °C for 48 h. [b] Conversion was determined by ¹H NMR spectroscopy using toluene as an internal standard. Bold entries indicate reactions with higher efficiencies. [c] In parenthesis: overall conversion of the electrophile where more than 10% formation of symmetrical ether were observed. [d] The reactions were repeated at least twice to confirm the reproducibility of the observed yield. [e] In parenthesis: overall conversion of *tert*-butyl alcohol to product and isobutylene determined by ¹H NMR spectroscopy. [f] 20 mol% with respect to the electrophile was used.

For thiophenol **2a**, the benzylic and allylic substrates **1ac** were the most selective electrophiles in the catalytic thioetherification reaction. Lewis acids generally performed well in the thioetherification reaction, and Bi^{III} showed the highest reactivity and also generated the desired products **3ac** in 86–99% conversions. Other catalysts showed moderate to good reactivity for these three electrophiles using the same reaction conditions. For substrates **1a**-**c**, homoetherification was observed for Pd^{II}, Au^{III}, La^{III}, Re^{VII} and HCl, which generated the symmetrical ether product in up to 30% yield. No regioisomers were observed in the reaction

Catalytic Nucleophilic Substitution by C-Centered Nucleophile **2 b**

The results from the C–C bond-forming reactions are given in Table 3. The reactions were run under three different reaction conditions depending on the electrophile. Reactions employing substrates **1a** and **1b** were run at room temperature for 10 h, **1c** was run at 60 °C for 10 h, and **1d** and **1e** were run at 80 °C for 10 h. To our knowledge, only Fe^{III[7c,o]} and Pd^{0[19k]} have been reported to be active in the nucleophilic substitution of **2b**.

For the carbon nucleophile **2b**, the allylic substrate **1b** showed the highest selectivity for forming the desired product. Except for Re^I and Re^{VII}, most

catalysts generated the desired product **4b** in 49–88% conversion in less than 10 h. Generally, the Lewis acids gave higher yields than the redox metals, where Bi^{III} and Fe^{III} gave 88% and 87% product yield, respectively. Au^{III}, which has never been reported to catalyze C–C bond-forming reactions using **2b**, generated the desired product in 80% yield. Interestingly, Pd^{II} produced the product in 74% yield. The mineral acid also catalyzed the C–C bond-forming reaction, though it generated the product in a lower yield.

The primary benzylic alcohol **1a** was the second most selective alcohol in the C–C bond-forming reaction with **2b** as

Catalytic Nucleophilic

Nucleophile 2 c

Substitution by O-Centered

The results from the etherifica-

tion by 3-phenylpropanol 2c

are given in Table 4. The reac-

tions were run under three dif-

ferent reaction conditions de-

pending on the electrophile.

Reactions employing substrates

1a and 1b were run at room

temperature for 10 h, 1c was

run at 60 °C for 6 h, and 1d and

1e were run at 90°C for 10 h.

All catalysts in this study have been reported to be active in

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2h

Scheme 6. Stabilization of **2b** by Lewis acidic catalysts.

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Table 3. Conversion in the catalytic nucleophilic substitution of alcohols (1) by acetylacetone (2b).^[a,b]



[a] The reactions were run using alcohol 1 (1 mmol), 2b (1 mmol) in nitromethane (2.5 mL), and metal catalyst (5 mol%). Reactions to form 4a,b were run at room temperature for 10 h. The reaction to form 4c was run at 60 °C for 10 h. Reactions to form4d,e were run at 80 °C for 10 h. [b] Conversion was determined by ¹H NMR spectroscopy using toluene as an internal standard. Bold entries indicate reactions with higher efficiencies. [c] The reactions were repeated at least twice to confirm the reproducibility of the observed yield. [d] In parenthesis: overall conversion of *tert*-butyl alcohol to product and isobutylene determined by ¹H NMR spectroscopy. [e] In parenthesis: overall conversion of the electrophile where more than 10% formation of symmetrical ether was observed. [f] 20 mol% with respect to the electrophile was used.

nucleophile and showed similar but lower efficiency than the allylic substrate to generate **4a** in 30–67% yield. La^{III}, Re^{VII}, and Re^I generated a substantial amount (23%, 30%, and 19%) of the symmetrical ether of **1a**.

The secondary benzylic alcohol **1c** required heating at 60 °C and gave excellent yields of **4c** with Fe^{III}, Bi^{III} and Pd^{II}. Also, moderate reactivity of the Au^{III} catalyst was observed in generating the product. The other catalysts showed low or no activity in this reaction. The etherification to generate the symmetrical ether was a major side reaction in almost all cases where lower yield of product **4c** was observed. The symmetrical ether may be an intermediate for many catalysts in this transformation. It should be noted that Re^{VII} was not active in this transformation; instead, the symmetrical ether was generated in 25 % yield.

Propargylic alcohol **1e** was a poor substrate in this transformation and required heating to 80°C for 10 h. Using either Fe- or Bi-based catalysts generated the desired product **4e** in a 38% yield, and the symmetrical ether was observed as a by-product, especially with the Re- and Labased catalysts.

Substrate **1d** was even more challenging. After heating the reaction mixture to 80 °C overnight, no conversion to **4d** was observed with any of the catalysts in this study, whereas water elimination from *tert*-butyl alcohol was found to be operating for all catalysts except bismuth, giving rise to the formation of volatile isobutylene in 22–81 % conversion. A possible explanation for the higher reactivity of the Lewis acids and Pd^{II} is that both the electrophile and the nucleophile are activated by the catalyst. The catalyst stabilizes the activated enolate ion and may form a chelated complex **2b**' (Scheme 6). etherification reactions.

Generally, the redox metals and La^{III} were more efficient in term of selectivity in generating the desired ethers than the other Lewis acids. For both 1a and 1b, the Re-based catalysts and also the La catalyst were the most efficient in the etherification reaction to generate products 5a,b. In the reaction of 1a, the symmetrical ether was generated in 20-30% as a side product in the case of both catalysts. The allylic substrate was more reactive than the primary benzylic substrate, and both rhenium-based catalysts generated 5b in 62-66% conversions and 5a in 46-57% conversion. The Pdbased catalyst was efficient in the transformation of the allylic electrophile, but not for transformation of the primary benzylic electrophile. Generally, the mineral acid and the Lewis acids were not efficient in the transformation of allylic and primary benzylic substrates using these reaction conditions.

The secondary benzylic alcohol **1c** required heating to 60 °C for 6 h in the etherification to generate **5c**. Substrate **1c** gave relatively good conversions, and Re^I and Au^{III} showed highest reactivity. Up to 20% symmetrical ether was observed when La^{III}, Re^{I,VII}, and HCl were employed as catalysts.

The least selective electrophiles to form the desired substitution products were the propargylic and tertiary aliphatic alcohols. These substrates required higher reaction temperatures and longer reaction times than the other substrates. In general, the propargylic alcohol was slightly more reactive than the tertiary alcohol. La^{III}, Re^I, Re^{VII} and Bi^{III} gave high rates of conversion to **5e** (60–76%). Remarkably, the Pd^{II} catalyst was not efficient in this transformation. We found that when the acetonitrile ligands were exchanged for stronger donor ligands (phenanthroline or triphenylphosphine)

For benzamide **2d**, the allylic alcohol **1b** was the most efficient electrophile and was amidated at room temperature by

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Table 4. Conversion in the catalytic nucleophilic substitution of alcohols (1) by 3-phenyl propanol (2c).^[a,b]

	OH R ¹ → R ² 1a-e	+ HO ⁺ Ph ⁻ 2c	5 mol% [M] MeNO ₂ 0 ⁴ R ¹ 5a-e	$\gamma_{\rm Ph}^{n=3}$ + H ₂ O R ²	
Products	Ph 5b	PMP ^{Oⁿ⁼³Ph 5a}	0 ⁽¹⁾ Ph Ph 5c	$Ph = O^{(n=3)} Ph = 5e^{5e}$	→
Catalysts					
FeCl ₃	0%	0%	trace	54 % ^[c]	23% (87%) ^[d]
BiBr ₃	0%	0%	68 %	64 % ^[c]	41 %
NaAuCl ₄ ·2H ₂ O	0%	31 %	76 % ^[c]	45 % ^[c]	34% (59%) ^[d]
La(OTf) ₃	67 % ^[c]	19%	42% (62%) ^[c,e]	76 % ^[c]	30% (83%) ^[d]
[PdCl ₂ (MeCN) ₂]	58 % ^[c]	Trace	59%	0%, ^[c] $30%$ ^[f]	51% (60%) ^[d]
[ReBr(CO) ₅]	66 % ^[c]	46 % ^[c]	78 % ^[c]	71 % ^[c]	52 % (79 %) ^[d]
MeReO ₃	62 % ^[c]	57 %	64%	60 % ^[c]	48 % (70 %) ^[d]
HCl ^[g]	0%	0%	37% (47%) ^[e]	52 % ^[c]	21% (38%) ^[d]

[a] The reactions were run using alcohol 1 (1 mmol), 2b (1 mmol) in nitromethane (2.5 mL), and metal catalyst (5 mol%). Reactions to form 5a, b were run at room temperature for 10 h. The reaction to form 5c was run at 60 °C for 6 h. Reactions to form 5d, e was run at 90 °C for 10 h. [b] Conversion was determined by ¹H NMR spectroscopy using toluene as an internal standard. Bold entries indicate reactions with higher efficiencies. [c] The reactions were repeated at-least twice to confirm the reproducibility of the observed yield. [d] Overall conversion in parenthesis of *tert*-butyl alcohol to product and isobutylene determined by ¹H NMR spectroscopy. [e] Overall conversion in parenthesis of the electrophile where more than 10% formations of symmetrical ether were observed. [f] Phenantroline and OTf was used as ligands. [g] 20 mol% with respect to the electrophile was used.

and the chlorides were exchanged for the less coordinating triflates, **5e** was generated in 30% yield after 10 h (Scheme 7). Still, only one regioisomer was formed.

The tertiary alcohol **1d** was the least efficient substrate in the etherification reaction to form the desired substitution product. Re^{I,VII} and Pd^{II} performed the reaction the best, and ether **5d** was generated in 48–52% conversions. A possible hypothesis for the higher efficiency of the redox metals in the etherification reaction is that a hydrogen-borrowing mechanism is operating. We concluded by experiment that this was not the case (see the Supporting Information). In addition to formation of the desired product, an appreciable amount of isobutylene was observed by water elimination of *tert*-butyl alcohol (see the Supporting Information for details).

Catalytic Nucleophilic Substitution by N-Centered Nucleophile **2** *d*

The results from the amidation reactions are given in Table 5. The reactions were run under three different reaction conditions depending on the electrophiles; **1b** was run at room temperature for 10 h, **1a** and **1d** were run at 80 °C for 12 h, and **1c** and **1e** were run at 100 °C for 12 h. All catalysts except Re^{I} have been reported to be active in C–N bond-forming reactions.

Bi^{III} catalysis. After 10 h, 59 % of 6b was obtained. All other catalysts gave no or low rates of conversion to product at this temperature. However, at higher reaction temperatures, most other catalyst showed moderate to good reactivity. The generation of the allylic cation was previously reported by Jana et al.,^[7i] who employed two diastereomeric allylic alcohols, one having a hydroxy group to the more hindered side near the Ph group and another having a hydroxy group at the less hindered side. They observed the formation of same product catalyzed by Fe^{III} salt in nitromethane solvent, which supports the formation of the

allylic cation during the course of the reaction.

The second most selective electrophile in the amidation reaction was the tertiary alcohol **1d**. Interestingly, this substrate showed less efficiency towards product formation for the other nucleophiles in this study. The tertiary alcohol was amidated by **2d** at 80 °C by both Fe^{III} and Bi^{III} catalysis. After 10 h, the product **6d** was formed in 31% and 52% yield, respectively. No other catalyst was efficient for amidation of **1d** under these reaction conditions. In analogy to the other transformations using **1d**, isobutylene formation was a major side reaction for all the catalyst except bismuth (see the Supporting Information for details).

The secondary benzylic alcohol **1c** was amidated at 100 °C and the reactions were run for 12 h. Fe^{III} and Bi^{III} were the most efficient and gave **6c** in 47 % and 48 % of conversions, respectively. Re^I, Au^{III}, and Pd^{II} were also reactive and gave **6c** in 29–36 % conversion. In the case of Re^I, the desired product was generated in 35 % yield. This Re^I-catalyzed C– N bond-forming reaction has not been reported before. La^{III}, Re^{VII}, and HCl showed low reactivity in the amidation reaction of **1c**. La^{III}, Re^I, and HCl produced the symmetrical ether in 31–45 % conversion. Primary benzylic alcohol **1a** was amidated at 80 °C with all catalysts except Fe^{III} to generate **6a** in low yields. Bi^{III} showed the highest catalytic activity and generated the product in 43 % yield after 12 h. The



other catalysts generated the product in 17–31% of conversions.

The propargylic alcohol **1e** was the least reactive alcohol in the amidation reactions. Only Fe^{III} and Bi^{III} showed any reac-

Scheme 7. Donating dative ligands and less-coordinating triflate ligand on palladium are necessary for reactivity in etherification of **1e**.

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cleophile, PdII and ReVII gave

moderate rates of conversion whereas Re^I performed poorly. In the case of the C-centered nucleophile, only Pd^{II} was active. For the O-centered nucleophile, all redox metals performed with high efficiency. For the N-centered nucleophile, Re^I performed better than both Pd^{II} and Re^{VII}. Formation of volatile isobutylene was observed as major side product for most of the reactions employing tertbutyl alcohol (1d) as electrophile, except in the case of bismuth (see the Supporting Infor-

mation for details). This could

be an explanation why bismuth

was efficient to produce rela-

tively high conversion of the

desired products with most of

the nucleophiles involving **1d** as electrophile compared to

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Table 5. Conversion in the catalytic nucleophilic substitution of alcohols (1) by benzamide (2d).^[a,b]

	OH R ¹ └──R ² 1a-e	+ $H_2N \xrightarrow{O} Ph \frac{5 \text{ m}}{M}$	$ \stackrel{ol\%}{\stackrel{[M]}{\underset{e}{\text{NO}_2}}} \stackrel{R^1}{\underset{R^2}{\overset{O}{\underset{H}{}}}} \stackrel{O}{\underset{H}{}} $	Ph + H ₂ O	
Products	Ph 6b	N H Ph H 6d	PMP N Ph H 6a	Ph NH Ph Ph 6c	Ph-=
Catalysts					
FeCl ₃	43 % ^[c]	31% (84%) ^[d]	0%	47 %	20%
BiBr ₃	59 % ^[c]	52 %	43 %	48 %	13%
NaAuCl ₄ ·2H ₂ O	25 % ^[c]	$0\% (41\%)^{[d]}$	31 %	36 %	0%
La(OTf) ₃	0%	$0\% (81\%)^{[d]}$	21 %	trace (45%) ^[e]	trace
[PdCl ₂ (MeCN) ₂]	28%	$0\% (18\%)^{[d]}$	27 % ^[c]	29 %	0%
[ReBr(CO) ₅]	0%	10% (76%) ^[d]	31 %	35 % ^[c]	0%
MeReO ₃	0%	trace (50%) ^[d]	28%	$0\% (37\%)^{[c,e]}$	0%
HCl ^[f]	0%	$0\% (22\%)^{[d]}$	17%	11 % (31 %) ^[e]	0%

[a] The reactions were run using alcohol 1 (1 mmol), 2d (1 mmol) in nitromethane (2.5 mL) using metal catalyst (5 mol %). The reactions to form **6b** was run at room temperature for 10 h. Reactions to form **6a,d** were run at 80 °C for 12 h. Reactions to form **6c,e** were run at 100 °C for 12 h. [b] Conversion was determined by ¹H NMR spectroscopy using toluene as an internal standard. Bold entries indicate reactions with higher efficiencies. [c] The reactions were repeated at least twice to confirm the reproducibility of the observed yield. [d] In parenthesis: overall conversion of *tert*-butyl alcohol to product and isobutylene determined by ¹H NMR spectroscopy. [e] In parenthesis: overall conversion of the electrophile where more than 10% formation of symmetrical ether were observed. [f] 20 mol% with respect to the electrophile was used.

tivity towards desired product formation, where the former catalyst generated 6e in 20% conversion.

Synopsis

The aim of this study was to determine the efficiency of different metals in performing catalytic nucleophilic substitution of alcohols with respect to the electrophile as well as the nucleophile. In the following section, we conclude and discuss the reactivity of the metals with respect to electrophiles and nucleophiles.

No major deviations among the catalysts with regards to the electrophiles were observed in this study. The trend in Scheme 3 was consistent for all metals, regardless of the nucleophile. Furthermore, there was no observed difference in regioselectivity of any of the substrates. Even in the case of substrates with allylic or propargylic functionality, only substitution at the C-O position was observed. For the nucleophiles, general and specific differences between the metals were observed. Overall, Fe^{III}, Bi^{III}, and Au^{III} showed greater efficiency than the redox metals for S-, C-, and N-centered nucleophiles, and Pd^{II}, Re^I, Re^{VII}, and La^{III} showed higher efficiency for the O-centered nucleophile. Within the group of Lewis acids, Bi^{III} gave the best results, regardless of the nucleophile (except O-centered). Across the range of nucleophiles, Fe^{III} and Bi^{III} showed similar reactivity. Generally, Au^{III} was observed to perform with slightly lower efficiency than Fe^{III} and Bi^{III}. Interestingly, the use of La^{III} produced lower rates of conversion than the other Lewis acids for all nucleophiles except for the O-centered 2c.

Within the group of redox metals, the reactivity was also highly dependent on the nucleophile. For the S-centered nuother Lewis acids.

Interestingly, in this study, the efficiency of the reactions to generate the products was found to be highly dependent on the reactivity of the nucleophiles. Currently we are investigating the detailed mechanism, supported by theoretical calculations.

Conclusions

This study provides an objective overview over the factors that govern the reactivity in the catalytic nucleophilic substitution of alcohols. Surprisingly, there is no observed deviation in reactivity or regioselectivity between the catalysts and the electrophiles; that is, the ease to generate the carbocation from the alcohol substrate is what governs the conversion to the desired product, and not the catalyst.

However, there are several differences in reactivity and chemoselectivity with respect to the nucleophile in these reactions. We found that: 1) Re^{I,VII}, Pd^{II}, and La^{III} generally favor O-centered nucleophiles and 2) Fe^{III}, Bi^{III}, and Au^{III} give better results with the S-, C-, and N-centered nucleophiles.

Experimental Section

Representative experimental procedure for the synthesis of 1-(3-((E)-4-Phenylbut-3-en-2-yloxy)propyl)benzene (5 b):

Allylic alcohol **1b** (148 mg, 1 mmol), 3-phenyl propanol **2c** ($136 \mu L$, 1 mmol), and La(OTf)₃ (29 mg, 0.05 mmol) were stirred at room temperature in nitromethane (2.5 mL) under nitrogen for 10 h (see general screening procedure in the Supporting Information for details). Nitromethane was evaporated under reduced pressure and the crude reaction

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mixture was purified by silica-gel column chromatography to afford **5b** (162 mg, 0.61 mmol, 61 % yield of isolated product) as a colorless oil. IR (Neat): \tilde{v} =2930, 1722, 1453, 1097, 747, 696 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ =1.35 (d, 6.3 Hz, 3H, H-methyl), 1.87–1.96 (m, 2H, PhCH₂CH₂), 2.71 (dt, 2H, *J*=1.8 Hz, 7.2 Hz, 2H, PhCH₂), 3.34–3.41 (m, 1H, OCH₂), 3.50–3.57 (m, 1H, OCH₂), 3.96–4.01 (m, 1H, OCH₃). (dd, *J*=7.5 Hz, 16.2 Hz, 1H, H-olefin), 6.51 (d, *J*=15.9 Hz, 1H, H-olefin), 7.07–7.41 ppm (m, 10H, H-arom). ¹³C NMR (100 MHz, CDCl₃): δ =21.6, 31.5, 32.5, 67.5, 76.4, 125.7, 126.4, 127.5, 128.2, 128.4, 128.5, 128.9, 130.7, 132.2 ppm. HRMS: calcd. for C₁₉H₂₂NaO 289.1568; found: 289.1552. Elemental anal. (%) calcd. for C₁₉H₂₂O (266.38): C 85.67, H 8.32; found C 85.70, H 8.36.

The reaction yield was determined by NMR spectroscopy to be 67% before purification by taking out 100 μ L of the reaction mixture and using toluene as internal standard (see the Supporting Information).

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- [1] A. R. Katritzky, B. E. Brycki, Chem. Soc. Rev. 1990, 19, 83.
- [2] O. Mitsunobu, Synthesis 1981, 1.
- [3] DEAD is diethyl azodicarboxylate.
- [4] a) R. A. Sheldon, Pure Appl. Chem. 2000, 72, 1233; b) B. M. Trost, Science 1991, 254, 1471.
- [5] D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, Jr., J. L. Leazer, R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks, T. Y. Zhang, *Green Chem.* **2007**, *9*, 411.
- [6] Other methods include hydrogen borrowing, see, G. Guillena, D. J. Ramon, M. Yus, *Chem. Rev.* 2010, 110, 1611.
- [7] a) P. Salehi, N. Iranpoor, F. K. Behbahani, Tetrahedron 1998, 54, 943; b) V. V. Namboodiri, R. S. Varma, Tetrahedron Lett. 2002, 43, 4593; c) U. Jana, S. Biswas, S. Maiti, Tetrahedron Lett. 2007, 48, 4065; d) Y. Nishimoto, Y. Onishi, M. Yasuda, A. Baba, Angew. Chem. 2009, 121, 9295; Angew. Chem. Int. Ed. 2009, 48, 9131; e) S.-K. Xiang, L.-H. Zhang, N. Jiao, Chem. Commun. 2009, 6487; f) A. Mirzaei, S. Biswas, J. S. M. Samec, Synthesis 2012, 44, 1213; g) I. Iovel, K. Mertins, J. Kischel, A. Zapf, M. Beller, Angew. Chem. 2005, 117, 3981; Angew. Chem. Int. Ed. 2005, 44, 3913; h) Z.-P. Zhan, J.-l. Yu, H.-J. Liu, Y.-Y. Cui, R.-F. Yang, W.-Z. Yang, J.-P. Li, J. Org. Chem. 2006, 71, 8298; i) U. Jana, S. Maiti, S. Biswas, Tetrahedron Lett. 2008, 49, 858; j) U. Jana, S. Maiti, S. Biswas, Tetrahedron Lett. 2007, 48, 7160; k) U. Jana, S. Biswas, S. Maiti, Eur. J. Org. Chem. 2008, 5798; 1) Y. Zhao, S. W. Foo, S. Saito, Angew. Chem. 2011, 123, 3062; Angew. Chem. Int. Ed. 2011, 50, 3006; m) J. Michaux, V. Terrasson, S. Marque, J. Wehbe, D. Prim, J.-M. Champagne, Eur. J. Org. Chem. 2007, 2601; n) W. Yan, Q. Wang, Y. Chen, J. L. Petersen, X. Shi, Org. Lett. 2010, 12, 3308; o) S. Maiti, S. Biswas, U. Jana, Synth. Commun. 2010, 41, 243; p) S. Biswas, S. Maiti, U. Jana, Eur. J. Org. Chem. 2009, 2354.
- [8] a) S. Kobayashi, T. Ogino, H. Shimuzu, S. Ishikawa, T. Hamada, K. Manabe, Org. Lett. 2005, 7, 4729; b) F. Howard, S. Sawadjoon, J. S. M. Samec, Tetrahedron Lett. 2010, 51, 4208; c) Y. Nishimoto, M. Kajioka, T. Saito, M. Yasuda, A. Baba, Chem. Commun. 2008, 6396; d) H. Qin, N. Yamagiwa, S. Matsunaga, M. Shibasaki, Angew. Chem. 2007, 119, 413; Angew. Chem. Int. Ed. 2007, 46, 409; e) P. A. Evans, J. Cui, S. J. Gharpure, R. J. Hinkle, J. Am. Chem. Soc. 2003, 125, 11456; f) Z.-P. Zhan, W.-Z. Yang, R.-F. Yang, J.-L. Yu, J.-P. Li, H.-J. Liu, Chem. Commun. 2006, 3352; g) S. Biswas, S. Maiti, U. Jana, Eur. J. Org. Chem. 2010, 2861.
- [9] V. Gevorgyan, M. Rubin, S. Benson, J.-X. Liu, Y. Yamamoto, J. Org. Chem. 2000, 65, 6179.
- [10] S.-Y. Wang, S.-J. Ji, Synlett 2007, 2222.

- [11] a) M. Yasuda, T. Somyo, A. Baba, Angew. Chem. 2006, 118, 807; Angew. Chem. Int. Ed. 2006, 45, 793; b) M. Yasuda, S. Yamasaki, Y. Onishi, A. Baba, J. Am. Chem. Soc. 2004, 126, 7186; c) M. Yasuda, T. Saito, M. Ueba, A. Baba, Angew. Chem. 2004, 116, 1438; Angew. Chem. Int. Ed. 2004, 43, 1414.
- [12] a) A. B. Cuenca, G. Mancha, G. Asensio, M. Medio-Simón, *Chem. Eur. J.* 2008, *14*, 1518; b) V. Terrasson, S. Marque, M. Georgy, J.-M. Campagne, D. Prim, *Adv. Synth. Catal.* 2006, *348*, 2063; c) M. Georgy, V. Boucard, J.-M. Campagne, *J. Am. Chem. Soc.* 2005, *127*, 14180; d) W. Rao, P. W. H. Chan, *Chem. Eur. J.* 2008, *14*, 10486.
- [13] M. R. Luzung, D. F. Toste, J. Am. Chem. Soc. 2003, 125, 15760.
- [14] Y. Liu, R. Hua, H.-B. Sun, X. Qiu, *Organometallics* 2005, 24, 2819.
 [15] M. Noji, T. Ohno, K. Fuji, N. Futaba, H. Tajima, K. Ishii, *J. Org.*
- Chem. 2003, 68, 9340.
 [16] a) J. He, J. W. Kim, K. Yamaguchi, N. Mizuno, Angew. Chem. 2009, 121, 10072; Angew. Chem. Int. Ed. 2009, 48, 9888; b) Y. Inada, Y. Nishibayashi, M. Hidai, S. Uemura, J. Am. Chem. Soc. 2002, 124, 15172; c) Y. Nishibayashi, Y. Inada, M. Hidai, S. Uemura, J. Am. Chem. Soc. 2003, 125, 6060; d) Y. Nishibayashi, Y. Inada, M. Yoshikawa, M. Hidai, S. Uemura, Angew. Chem. 2003, 115, 1533; Angew. Chem. Int. Ed. 2003, 42, 1495; e) Y. Yamauchi, G. Onodera, K. Sakata, M. Yuki, Y. Miyake, S. Uemura, Y. Nishibayashi, J. Am. Chem. Soc. 2007, 129, 5175; f) Y. Nishibayashi, A. Shinoda, Y. Miyake, H. Matsuzawa, M. Sato, Angew. Chem. 2006, 118, 4953; Angew. Chem. Int. Ed. 2006, 45, 4835; g) A. B. Zaitsev, S. Gruber, P. A. Plüss, P. S. Pregosin, L. F. Veiros, M. Wörle, J. Am. Chem. Soc. 2008, 130, 11604.
- [17] Z. Zhu, J. H. Espenson, J. Org. Chem. 1996, 61, 324.
- [18] a) B. Blank, R. Kempe, J. Am. Chem. Soc. 2010, 132, 924; b) A. Prades, R. Corberan, M. Poyatos, E. Peris, Chem. Eur. J. 2008, 14, 11474.
- [19] a) K. J. Miller, M. M. Abu-Omar, *Eur. J. Org. Chem.* 2003, 1294;
 b) Y. Bikard, R. Mezaache, J.-M. Weibel, A. Benkouider, C. Sirlin, P. Pale, *Tetrahedron* 2008, 64, 10224; c) Y. Tamaru, *Eur. J. Org. Chem.* 2005, 2647; d) J. Muzart, *Tetrahedron* 2005, 61, 4179; e) J. Muzart, *Eur. J. Org. Chem.* 2007, 3077; f) T. Yamamoto, M. Akimoto, O. Saito, A. Yamamoto, *Organometallics* 1986, 5, 1559; g) S. Sawadjoon, J. S. M. Samec, *Org. Biomol. Chem.* 2011, 9, 2548; h) S. Sawadjoon, J. S. M. Samec, unpublished results; i) A. Lundstedt, J. S. M. Samec, patent application WO2012121659 (A1); j) S. Sawadjoon, A. Lundstedt, J. S. M. Samec, *ACS Catal.* 2013, in press, DOI: 10.1021/cs300785r; k) Y. Kayaki, T. Koda, T. Ikariya, *J. Org. Chem.* 2004, 69, 2595.
- [20] E. Emer, R. Sinisi, M. G. Capdevila, D. Petruzziello, F. De Vincentiis, P. G. Cozzi, *Eur. J. Org. Chem.* 2011, 647.
- [21] a) H. Mayr, B. Kempf, A. R. Ofial, Acc. Chem. Res. 2003, 36, 66;
 b) H. Mayr, M. Patz, Angew. Chem. 1994, 106, 990; Angew. Chem. Int. Ed. Engl. 1994, 33, 938; c) C. Schindele, K. N. Houk, H. Mayr, J. Am. Chem. Soc. 2002, 124, 11208; d) H. Mayr, O. Kuhn, M. F. Gotta, M. Patz, J. Phys. Org. Chem. 1998, 11, 642; e) H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R. Loos, A. R. Ofial, G. Remennikov, H. Schimmel, J. Am. Chem. Soc. 2001, 123, 9500; f) S. Minegishi, S. Kobayashi, H. Mayr, J. Am. Chem. Soc. 2004, 126, 5174; g) H. Mayr, A. R. Ofial in Carbocation Chemistry (Eds.: G. A. Olah, G. K. S. Prakash), Wiley, Hoboken, NJ, 2004, chap. 13, p. 331; h) S. T. A. Berger, F. H. Seeliger, F. Hofbauer, H. Mayr, Org. Biomol. Chem. 2007, 5, 3020; i) M. Baidya, G. Y. Remennikov, P. Mayer, H. Mayr, Chem. Eur. J. 2010, 16, 1365.
- [22] a) C. P. Casey, C. S. Yi, J. Am. Chem. Soc. 1992, 114, 6597; b) C. P. Casey, A. D. Selmeczy, J. R. Nash, C. S. Yi, D. R. Powell, R. K. Hayashi, J. Am. Chem. Soc. 1996, 118, 6698; c) C. P. Casey, T. M. Boller, J. S. M. Samec, J. R. Reinert-Nash, Organometallics 2009, 28, 123.
- [23] S. Biswas, J. S. M. Samec, Chem. Commun. 2012, 48, 6586.

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