Stereoselective Alkylation of (S)-N-Acyl-4-isopropyl-1,3-thiazolidine-2-thiones Catalyzed by (Me3P)2NiCl2

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ABSTRACT:

The structurally simple (Me3P)2NiCl2 complex catalyzes SN1-type alkylations of chiral N-acyl thiazolidinethiones with diarylmethyl methyl ethers and other stable carbenium cations. The former can contain a variety of functional groups and heteroatoms at the α-position. The resultant adducts are isolated as single diastereomers in high yields and can be converted into enantiomerically pure derivatives in a straightforward manner

The asymmetric C-α-alkylation of carbonyl compounds is one of the most valuable tools for the stereoselective construction of carbon−carbon bonds.1 Conventional alkylations proceed through an SN2-type mechanism and thus require highly nucleophilic species, such as metal enolates or enamines, together with sterically nonhindered and activated alkyl halides or sulfonates. Despite the tremendous accomplishments achieved in this area, the need to expand the scope of such transformations has recently triggered the introduction of a variety of new concepts. Indeed, MacMillan devised highly enantioselective α-alkylations of aldehydes based on a new SOMO activation mode,2 which was later enhanced by merging photoredox catalysis with organocatalysis.3,4 Zakarian exploited the biradical character of titanium enolates5 for dual Ti−Ru catalysis in the direct radical haloalkylation of chiral oxazolidinones. 6 In turn, Jacobsen reported enantioselective SN1-type additions of silyl ketene acetals to prochiral oxocarbenium intermediates generated catalytically by anion binding of chiral thioureas to glycosyl chlorides.7,8 Besides this, Jacobsen,9 Melchiorre,10 and Cozzi11 also reported organocatalytic alkylations of aldehydes with diarylmethyl derivatives, which presumably proceed through an SN1-type mechanism.12 More recently, Jorgensen has devised an insightful strategy for the asymmetric alkylation of aldehydes based on the 1,6-conjugated addition of chiral enamines to p-quinone methides, which permits the simultaneous installation of two new stereocenters. 13,14

Taking advantage of these precedents and our own experience in this field,15 we envisaged that chiral N-acyl thiazolidinethiones might undergo highly stereoselective SN1 direct type alkylations catalyzed by structurally simple, commercially available, and easy to handle nickel(II) complexes.16,17 As shown in Scheme 1, the parallel generation of putative nickel(II) enolates by the action of (R3P)2NiL2 catalysts and carbocationic intermediates by Lewis acid treatment of appropriate E−X substrates might provide the required partners for the desired alkylations. If such a reaction occurs, the outstanding stereocontrol imparted by the thiazolidinethione scaffold on the configuration of the α-chiral center18 could produce a single diastereomer of the alkylated adduct that could eventually be converted into a plethora of enantiomerically pure derivatives by removal of the chiral auxiliary.19

Preliminary experiments with (S)-4-isopropyl-N-propanoyl-1,3-thiazolidine-2-thione (1), 4,4′-dimethoxybenzhydrol, (Me3P)2NiCl2 as the catalyst, TESOTf as the Lewis acid, and 2,6-lutidine as the base did not furnish the desired alkylated adduct even after long reaction times (entry 1 in Table 1). Considering that the lack of reactivity could be due to the poor nature of the OH as the leaving group, parallel alkylations with a variety of derivatives were next assessed. Silyl protected 4,4′-dimethoxybenzhydrol also proved to be completely unreactive (entry 2 in Table 1); but we were pleased to observe that the corresponding methyl ether afforded alkylated adduct 2a in a 94% yield, as a single diastereomer (entry 3 in Table 1). Hav identified the appropriate leaving group, we then examined the influence of catalyst loading and reaction time.20 The reaction turned out to be much faster than expected: alkylated adduct 2a was isolated in an excellent yield after just 1 h (compare entries 3−4 in Table 1). It should be noted that the reaction was also completed using 2.5 and 1 mol % and afforded 2a in a yield of up to 93% after 15 h (entries 5−6 in Table 1) and indeed at shorter reaction times (entry 7 in Table 1). Smaller amounts of catalyst were unable to mediate quantitative conversions even after long reaction times, but a tiny 0.5 mol % load was enough to produce 2a in a remarkable 71% yield after 48 h (entry 8 in Table 1). This indicates that the catalyst attains an outstanding turnover value of ca. 140. Finally, the reaction did not take place in absence of (Me3P)2NiCl2 (entry 9 in Table 1). All together, these results prove that alkylation of 1 with 4,4′-dimethoxybenzhydryl methyl ether is catalyzed by 1−5 mol % of (Me3P)2NiCl2 to produce adduct 2a as a single diastereomer in 92−94% yield in a simple and very efficient manner.

All these reactions were carried out at a 0.5 mmol scale; but they could easily be scaled-up. Indeed, alkylated adduct 2a was prepared in a 92% yield at the 5 mmol scale (2.05 g) from 1.2 equiv of the methyl ether after keeping the reaction mixture in the freezer (−20 °C). Moreover, the chiral auxiliary was removed in a straightforward manner to obtain enantiomerically pure alcohol and morpholine amide derivatives in high yields, as shown in Scheme 2.21

Once the synthetic potential of such an alkylation was established, the optimized conditions were then applied to a wide range of diarylmethyl methyl ethers. The outcome of these alkylations proved to be strongly dependent on the substituents on the aromatic rings; so the conditions reported in entry 3 of Table 1 were applied. As represented in Scheme 3, the reaction gives excellent yields, provided that the electrophile contains electronically rich aromatic rings. Indeed, substrates containing one or two ether, thioether, or amine groups on the aryl moiety produced the alkylated adducts 2 as single diastereomers in yields of up to 96%.22 The less stabilized methyl substituted counterpart in contrast just afforded adduct 2e in a poor 10% yield, and the simple benzhydryl methyl ether did not react at all.

Running parallel to these reactions, N-acyl thiazolidinethiones 5−13 shown in Scheme 4 were smoothly alkylated with 4,4′- dimethoxybenzhydryl methyl ether to afford adducts 14a−22a as single diastereomers in excellent yields. The alkylation was not affected by the steric hindrance of R, and even thiazolidinethione 7, which possesses a bulky isopropyl group, produced adduct 16a in a 94% yield. The presence of neither an alkene nor an ester group in R was not a problem, and adducts 17a and 18a were obtained in similar yields. Importantly, the alkylation also succeeded with thiazolidinethiones containing heteroatoms at the α-position, and adducts 19a−22a were isolated in a yield of up to 95%, which represents a new and highly appealing way to prepare enantiomerically pure α-oxygenated and α-nitrogenated carbonyl compounds. Finally, X-ray analysis of 14a permitted us to firmly establish the absolute configuration of all these adducts.23

A plausible mechanism for the above alkylations is outlined in Scheme 5. Since Sodeoka uncovered the formation of nickel(II) triflate complexes by treatment of the corresponding nickel(II) chlorides with TESOTf,24 (Me3P)2Ni(OTf)2 may be the true catalyst of the alkylation reaction. Thus, addition of this complex to 1 gives rise to complex I, which can be deprotonated by 2,6- lutidine to produce chelated Z enolate II. The crucial step in the overall cycle involves the production of the carbenium intermediate, [R1]+. If such a species can be generated in situ from R1−OMe and TESOTf, the isopropyl group at C4 hinders the approach of the Re face of the enolate to the [R1]+ cation and facilitates the stereocontrolled construction of the carbon−carbon bond in III. Finally, product dissociation regenerates the catalyst and furnishes diastereomerically pure alkylated adduct 2.25

As the stability of [R1]+ species can be anticipated by application of Mayr's scale,26 other carbenium ions were then identified as potential candidates to undergo the aforementioned reactions. Taking advantage of such a predictive tool and aiming to expand the scope of the process, we examined the alkylation of N-propanoyl thiazolidinethione 1 with methyl trityl ether and tropylium tetrafluoroborate (C7H7BF4). The former substrate involves a bulky electrophile, the trityl cation, which represents a challenging case for any asymmetric alkylation; whereas the second reagent is a commercially available salt that does not require further activation. The results shown in Scheme 6 met our expectations. The trityl derived adduct 2g was isolated with a 22% yield, far below the common yields reported in Scheme 4, but acceptable if one considers the steric bulk of trityl carbocation. In turn, diastereomerically pure tropylium adduct 2h was isolated in a 74% yield, which proves that the alkylation described here can be extended to different substrates provided that the corresponding carbenium intermediates are generated in situ or added to the reaction mixture.

In summary, the structurally simple and easy to handle (Me3P)2NiCl2 complex catalyzes SN1-type alkylations of chiral N-acyl thiazolidinethiones with methyl ethers activated by TESOTf. Importantly, just 1−5 mol % of the nickel(II) complex is enough to achieve excellent yields. The acyl group can contain a variety of alkyl substituents, functional groups, and heteroatoms at the α-position. In turn, the electrophile encompasses diarymethyl or trityl methyl ether, and stable carbenium cations such as the tropylium carbocation. The resultant adducts are isolated as single diastereomers, usually in high yields, and can easily be converted into enantiomerically pure derivatives by the removal of the chiral auxiliary under mild conditions.

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Notes

The authors declare no competing financial interest

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Legends to figures

Scheme 1. Direct SN1-Type Alkylations

Scheme 2. Removal of the Chiral Auxiliary from 2a

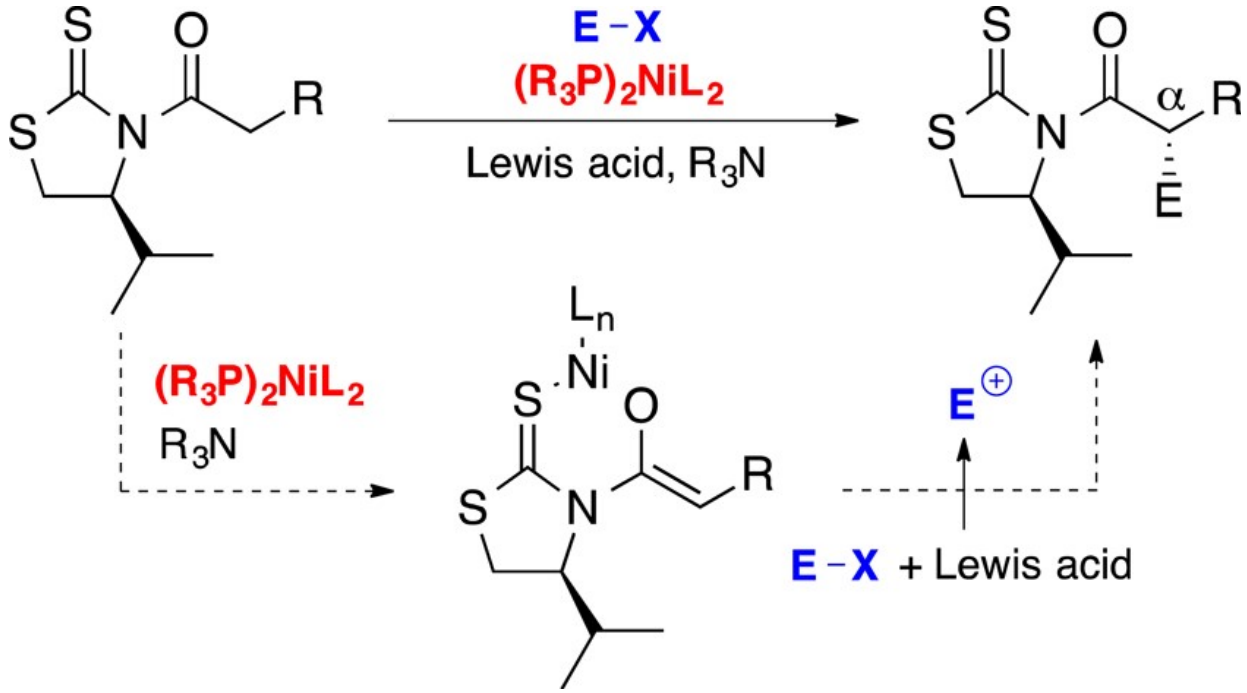
Scheme 3. Alkylation of 1 with Ar2CHOMe

Scheme 4. Alkylation of (S)-N-Acyl-4-isopropyl-1,3-thiazolidine-2-thiones

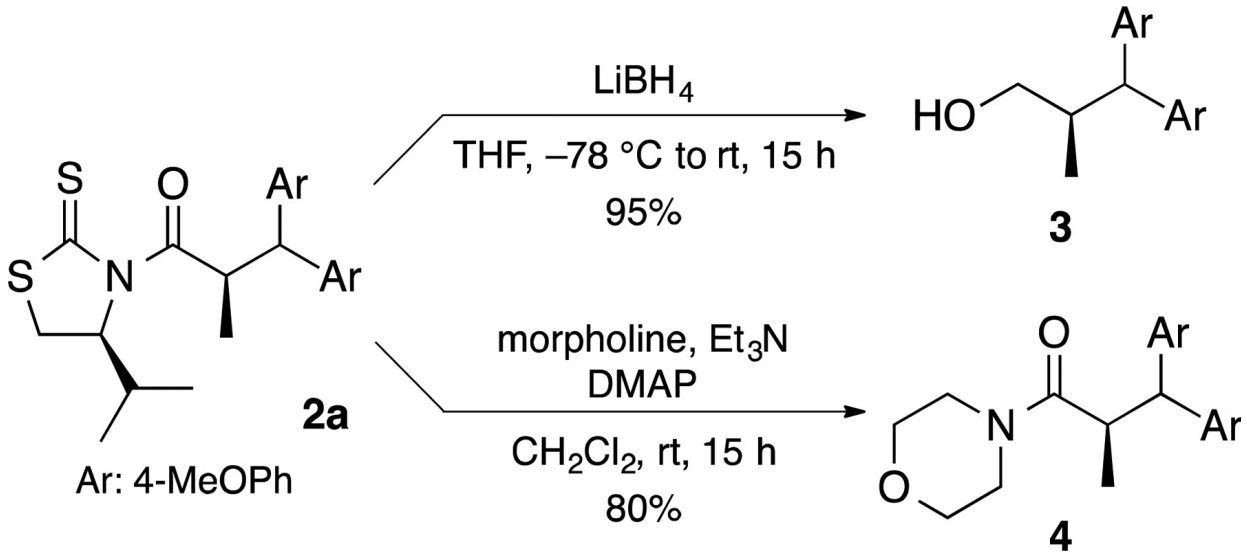
Scheme 5. Plausible Mechanism for the Stereocontrolled Catalytic Alkylation of 1

Scheme 6. Stereoselective Alkylations of 1

SCHEME 1.



SCHEME 2.


LiBH4
THF, –78 °C to rt, 15 h
95%
HO
Ar
Ar
3
S
O
Ar
S
N
Ar
2a
Ar: 4-MeOPh
morpholine, Et3N
DMAP
CH2Cl2, rt, 15 h
80%
O
Ar
N
Ar
O
4

238 **SCHEME 3**

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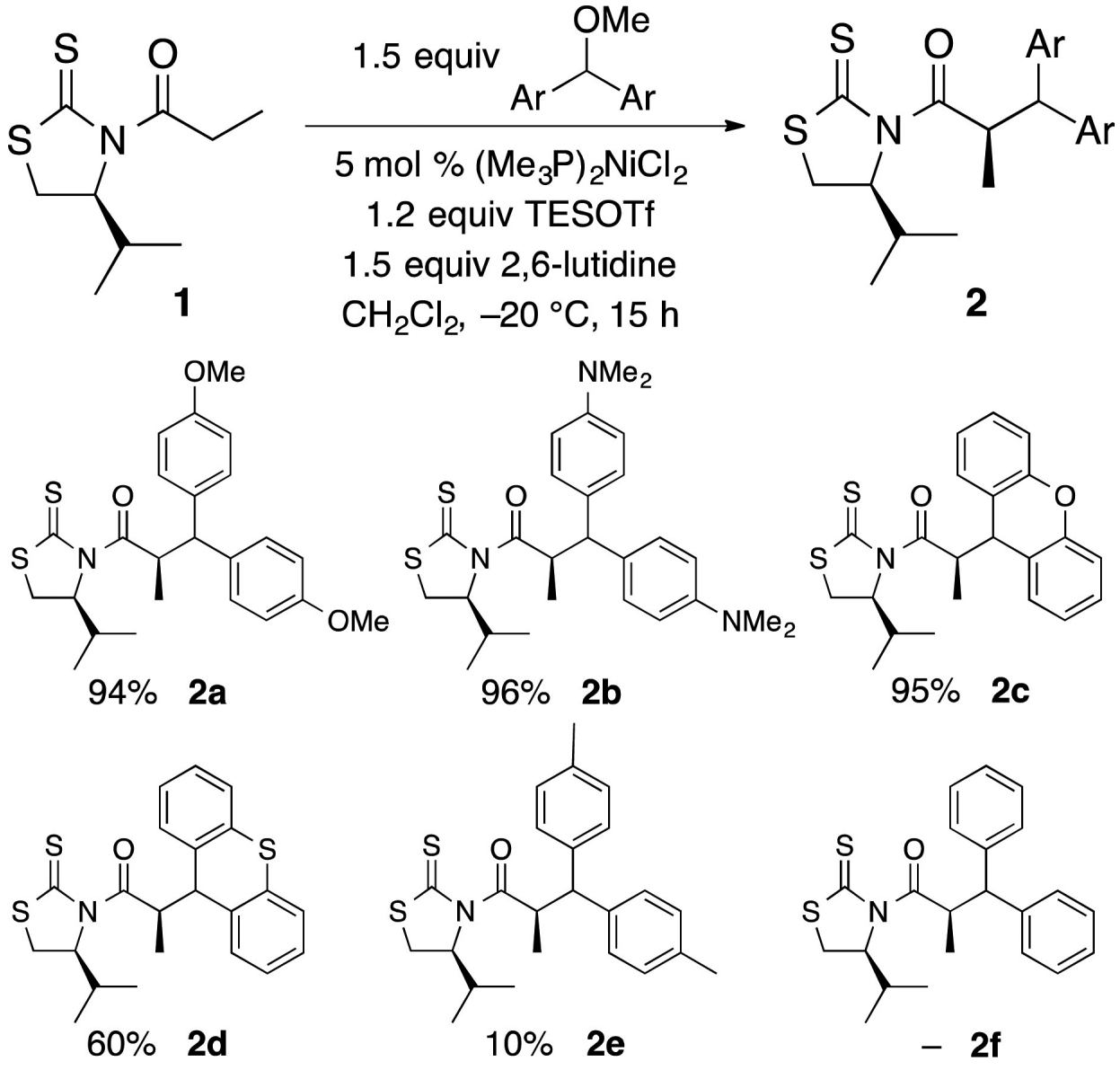
240



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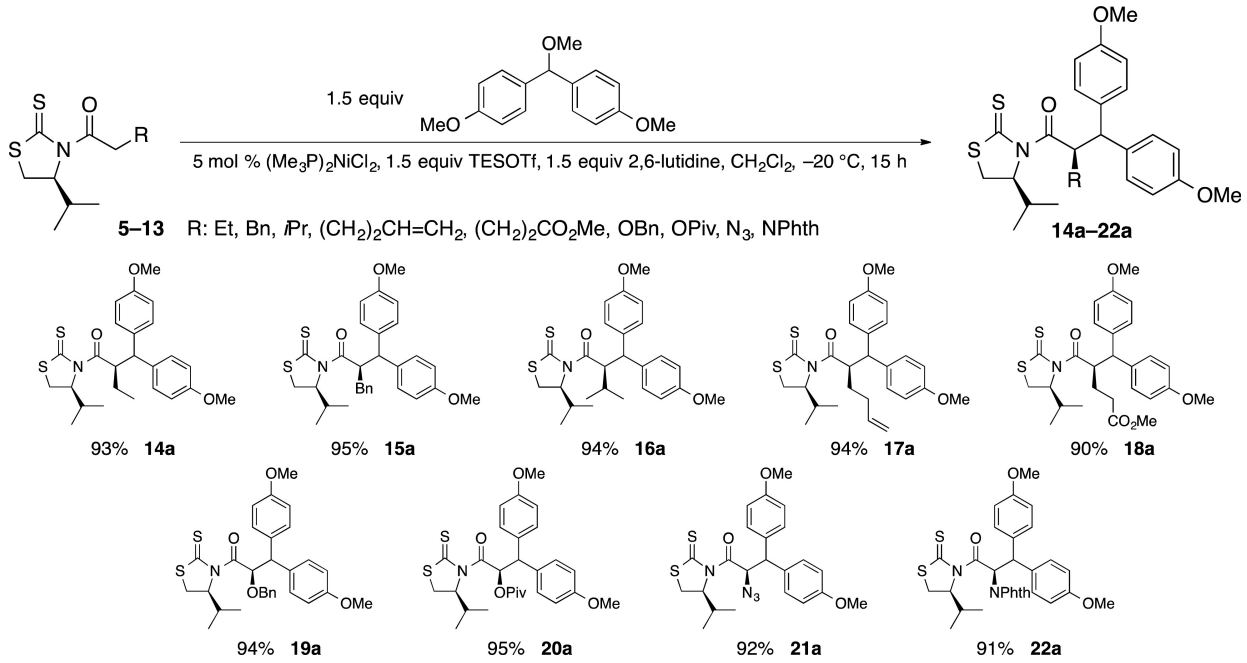
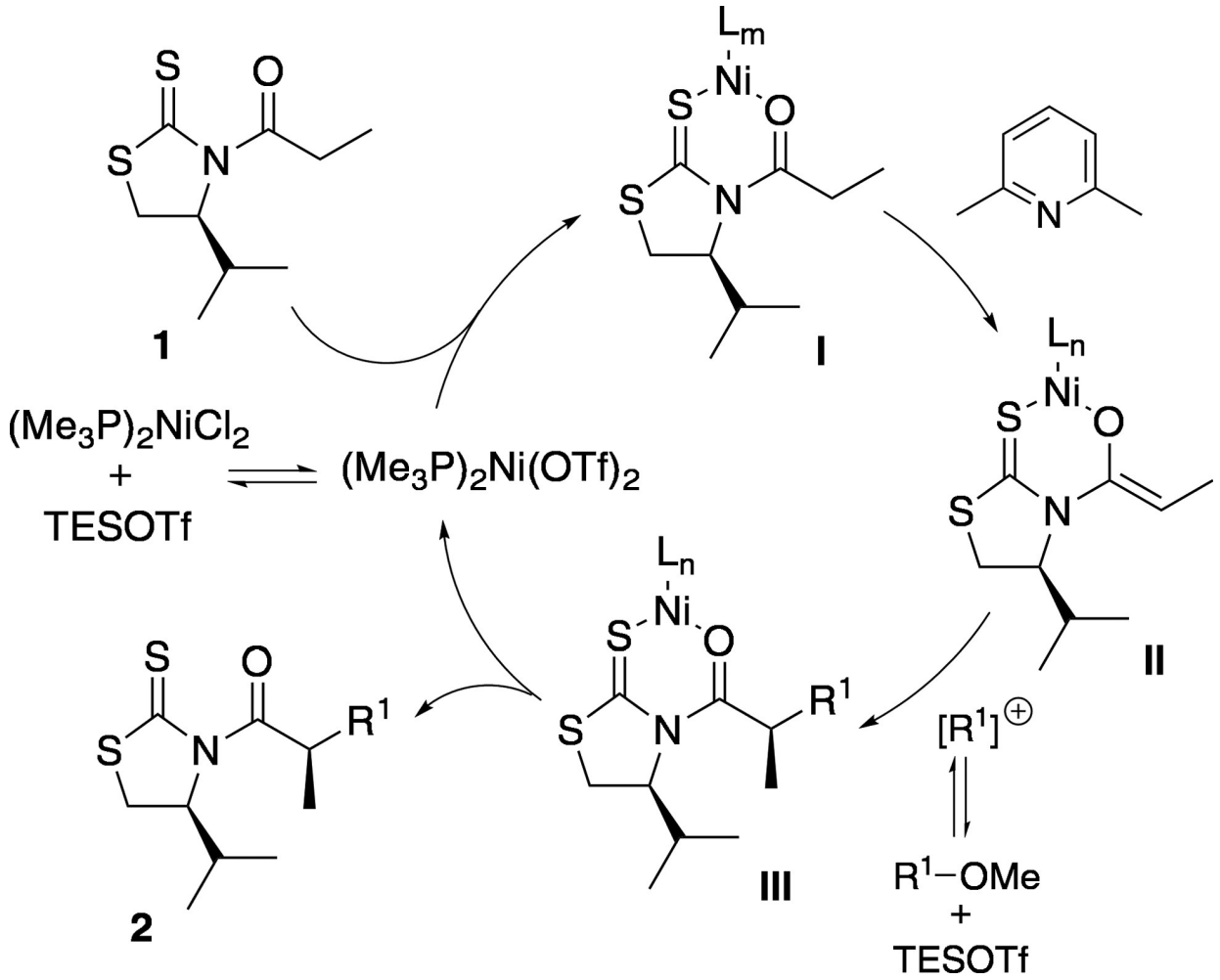
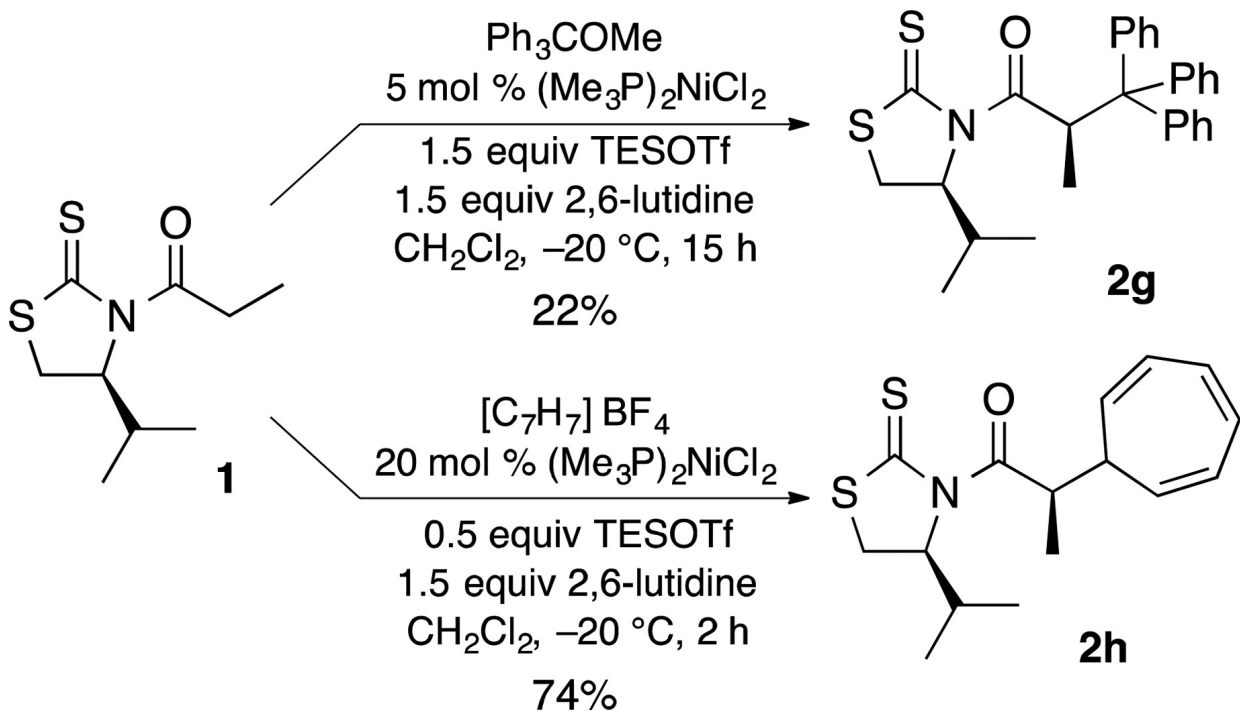
SCHEME 4


1.5 equiv
OMe
MeO
OMe
5 mol % (Me3P)2NiCl2, 1.5 equiv TESOTf, 1.5 equiv 2,6-lutidine, CH2Cl2, –20 °C, 15 h
5–13 R: Et, Bn, iPr, (CH2)2CH=CH2, (CH2)2CO2Me, OBn, OPiv, N3, NPhth
14a–22a
93% 14a
95% 15a
94% 16a
94% 17a
90% 18a
94% 19a
95% 20a
92% 21a
91% 22a

SCHEME 5.



SCHEME 6


Ph3COMe
5 mol % (Me3P)2NiCl2
1.5 equiv TESOTf
1.5 equiv 2,6-lutidine
CH2Cl2, –20 °C, 15 h
22%
2g
[C7H7] BF4
20 mol % (Me3P)2NiCl2
0.5 equiv TESOTf
1.5 equiv 2,6-lutidine
CH2Cl2, –20 °C, 2 h
74%
2h
1

263 **Table 1.** Preliminary Studies on the Alkylation of 1

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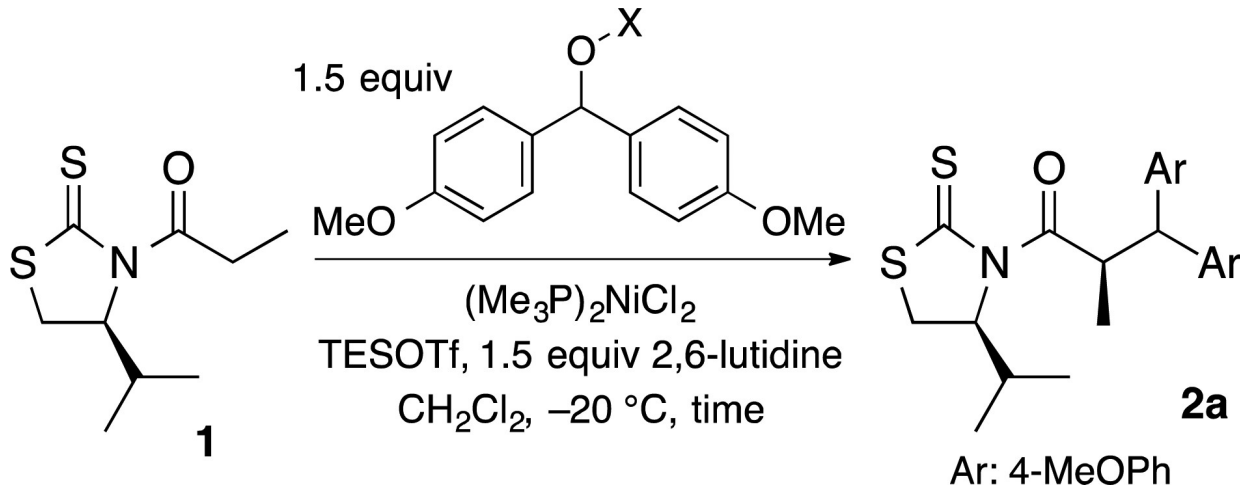

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entry	X	$(Me_3P)_2NiCl_2$ (mol %)	time (h)	yield 2a (%)[a]
1[b]	H	5	15	nr
2[b]	TES	5	15	nr
3[b]	Me	5	15	94
4[b]	Me	5	1	94
5[c]	Me	2.5	15	93
6[c]	Me	1	15	92
7[c]	Me	1	5	92
8[c]	Me	0.5	48	71[d]
9[c]	Me		72	nr

[a]Isolated yield after chromatographic purification. [b]1.2 equiv of TESOTf. [c]1.15 equiv of TESOTf. [d]25% of 1 was recovered.

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