Nickel-catalyzed, sodium iodide-promoted reductive dimerization of alkyl halides, alkyl pseudohalides, and allylic acetates†

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The first general method for the reductive dimerization of alkyl halides, alkyl mesylates, alkyl trifluoroacetates, and allylic acetates is reported which proceeds with low catalyst loading (0.5 to 5 mol%), generally high yields (80% ave yield), and good functional-group tolerance.

Many natural products are dimers or pseudodimers, and the ability of dimers to act as ligands for proteins or DNA and mediate cell function has been recognized.[1] Dimerization can increase affinity for biological targets, with significant consequences *in vivo*. For example, dimers of vancomycin[2] and its analogues[3] are able to inhibit the growth of bacteria resistant to monomeric vancomycin. Dimerization has also found use in the synthesis of interlocked molecules,[4] and in total synthesis.[5] As such, there is an increasing number of groups looking at the dimerization of a variety of natural products,[6] known drugs,[2] and drug-like molecules.[3,7] Because the nature of the linkage between the two monomers has a profound influence on the properties of the resultant dimers, there is a need for new dimerization reactions that complement those already available.

Methods for the mild, direct dimerization of olefins (olefin metathesis), carbonyls (pinacol coupling, McMurry coupling), and aryl halides (Ullmann reaction) are available,[8] *yet a general, mild method for the direct dimerization of alkyl halides has remained elusive*. Historically, Wurtz coupling was an important method for the dimerization of alkyl halides,[9] but yields with functionalized molecules were often unsatisfactory. More recently, methods mediated by stoichiometric (In or Cu) or catalytic (Pd, Fe, or Cu) amounts of metal have been developed,[10] but their scope and/or functional-group compatibility is limited. Overall, none of these reactions have been shown to tolerate functionalized substrates less reactive than alkyl iodides and the dimerization of even a simple substrate, such as 5-bromopentyl methyl ketone (Table 1, entry 9), is a challenge.

An alternative method to the reductive dimerization of alkyl halides is the conversion of a portion of the alkyl halide into an organometallic reagent, and subsequent coupling of the reagent with the remaining alkyl halide. While methods to achieve efficient Csp^3–Csp^3 bond formation by cross-coupling have recently been realized,[11] their application in the synthesis of *dimeric molecules* has several drawbacks. For example,

dimerization of 5-bromopentyl methyl ketone through the organozinc reagent[12] or the organoboron reagent[13] has strong literature precedent, but requires extra steps which are air and moisture sensitive. Direct reductive coupling of organic halides is more atom-economical than cross-coupling methods because no valuable organic halide is sacrificed in the synthesis of the corresponding organometallic reagent or wasted as excess reagent. Use of 1.2 to 3 equiv. of an organometallic reagent in the cross-coupling step would represent a loss of 9–50% of starting organic halide. Finally, cross-coupling reactions of alkyl sulfonate esters is a challenge[14] for many nickel-catalyzed methods[15] and the use of alkyl trifluoroacetate esters beyond benzyl esters in cross-coupling reactions has not, to our knowledge, been reported.[16]

Reductive methods for the coupling of unactivated alkyl halides with aryl halides that either form the organometallic reagent *in situ*[17] or appear to avoid intermediate organometallic reagent formation[18] have recently been developed, and we envisioned a mild, nickel-catalyzed dimerization of alkyl halides could be realized as an outgrowth of our work in this area. We report here a general, nickel-catalyzed solution to the problem of the dimerization of alkyl halides, alkyl pseudohalides, and allylic acetates that is mild (40–80 °C, no acid or base), proceeds at low catalyst loading (0.5 to 5 mol% catalyst), is unaffected by air or moisture (reactions run under air), and scales easily from 0.5 mmol to 40 mmol (Scheme 1).
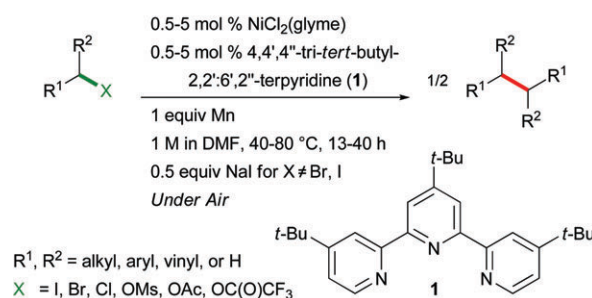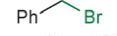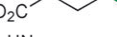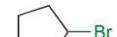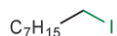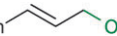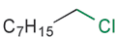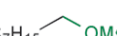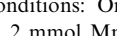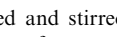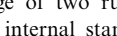

Scheme 1 Reductive dimerization of alkyl bromides.

Following an initial survey of nitrogen ligands,[19] we found that 4,4′,4″-tri-*tert*-butyl-2,2′:6′,2″-terpyridine, **1**,[20] is significantly better than any of the other ligands tested. This result is consistent with the work of Zhou and Fu,[21] Hu *et al.*,[22] and Vicic *et al.*,[20c–e] who have shown that tridentate amine ligands on nickel can produce catalysts that will form Csp^3–Csp^3 bonds efficiently. Further experiments showed that DMF was a superior solvent (DMF > DMAC > DMSO > NMP ~ DMI ~ DMPU ~ 2-butanol > THF > MeCN) and that catalyst loading could be lowered to 0.5 mol% (with

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Table 1 Scope of the reductive dimerization of alkyl bromides[a]

R–X $\xrightarrow[\text{1 equiv Mn} \atop \text{DMF, 40-80 °C, 13-40 h}]{\text{y mol \% NiCl}_2\text{(glyme)} \atop \text{y mol \% terpyridine } \mathbf{1}}$ 1/2 R–R

Entry	Substrate	y	Additive	t/h	Yield[b] (%)
1	In glove box (C_7H_{15}—Br)	0.5	—	17	98[c]
2	Under N_2 on benchtop	0.5	—	17	98[c]
3	Under air on benchtop	0.5	—	19	96[c]
4	Ph⌒⌒Br	0.5	—	17	97
5	Ph⌒Br	0.5	—	20	81
6	EtO_2C⌒⌒⌒Br	0.5	—	27	95
7	BocHN⌒⌒⌒Br	0.5	—	24	81[c]
8	CbzHN⌒⌒⌒Br	0.5	—	24	93
9	(ketone)⌒⌒⌒⌒Br	0.5	—	14	90[c]
10	Ph–CH(CH₃)Br	0.5	—	18	80[d]
11	cyclopentyl–Br	2	—	18	78
12	C_7H_{15}⌒I	2	—	17	94
13	Ph⌒Cl	2	—	20	81
14	Ph⌒⌒OAc	5	—	20	84[e]
15	cyclohexenyl–OAc	5	—	40	46[d]
16	C_7H_{15}⌒Cl	2	—	100	(20)
17[g]		2	NaI[f]	18	86
18	C_7H_{15}⌒OMs	2	—	13	(NR)
19		2	NaI[f]	21	82
20	Ph⌒OC(O)CF₃	2	—	13	(NR)
21		2	NaI[f]	15	57
22	C_7H_{15}⌒OC(O)CF₃	2	—	13	(NR)
23[g]		2	NaI[f]	21	35
24[g]		2	NaI[h]	25	45[c]

[a] Reaction conditions: On the benchtop, 2 mmol alkyl halide or pseudohalide, 2 mmol Mn powder, NiCl₂(glyme), and terpyridine **1** were combined and stirred in 2 mL of anhydrous DMF. [b] Isolated yields, average of two runs. Yields in parenthesis are GC yields, corrected vs. internal standard. NR = only sm and/or hydrolysis products observed. [c] Single run. [d] Product is a 1 : 1 mixture of diastereomers. [e] Crude product has a 94 : 6 [linear] : [other isomers] ratio. [f] 50 mol% NaI was added to the reaction. [g] At 80 °C. [h] 100 mol% NaI was added to the reaction.

respect to starting alkyl halide). Finally, while all initial work was conducted under strictly anhydrous and air-free conditions, it was found that *reactions set up on the bench and run under air provided nearly identical results to those set up in a glove box* (Table 1, entries 1–3).[23]

We applied the optimized conditions to a sampling of alkyl halides (Table 1) and found that the functional-group tolerance of the dimerization reaction is promising. Notably, common nitrogen protecting groups (*tert*-butoxycarbonyl, entry 7 and benzyloxycarbonyl, entry 8) and a ketone (entry 9) are well

tolerated. Secondary bromides can also be coupled in good yields (entries 10 and 11), but cyclopentyl bromide (entry 11) required a higher catalyst loading (2 mol%). No diastereoselectivity was observed in the formation of 2,3-diphenylbutane (entry 10).
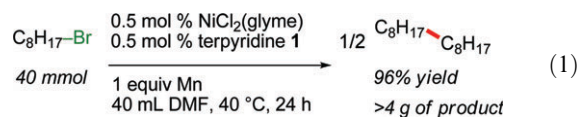
Allylic acetates are readily available, less reactive alternatives to allylic chlorides and bromides, but reports of the reductive dimerization of allylic acetates are rare.[24] Our optimized catalyst system accomplished this transformation for one representative linear and one cyclic allylic acetate (entries 14 and 15). 1,6-Diphenyl-1,5-hexadiene was formed in high yield, with only trace amounts of other isomers detectable by GC or NMR analysis. Previous reports of this dimerization noted poor selectivity for the all-linear product (50% or less selective).[24]

Extension of the dimerization reaction to substrates that are typically less reactive in nickel-catalyzed coupling reactions was investigated, but results were poor under standard conditions (entries 16, 18, 20, and 22). *With the simple addition of catalytic (50 mol%) sodium iodide, reactions of alkyl chlorides and alkyl mesylates were dramatically improved (entries 17 and 19)*. Alkyl sulfonate esters are typically unreactive in nickel-catalyzed cross-coupling processes[14,21] unless a nickelate species is generated.[15]

While benzyl trifluoroacetate esters have been shown to react in metal-catalyzed processes,[16] reactions of unactivated alkyl trifluoroacetate esters that cleave the alkyl–O bond are rare. *In the presence of sodium iodide, alkyl trifluoroacetates can be made to dimerize in moderate yield (entries 20–24)*. Because trifluoroacetates are simple to prepare and are not potent alkylating agents, their use in cross-coupling reactions merits further study.

The role of added iodide in these reactions is likely two-fold: (1) enhancement of the reductive coupling, possibly by facilitating reduction of the nickel catalyst[25] or the formation of a nickelate species,[15,26] and (2) generation of reactive alkyl iodides from unreactive alkyl trifluoroacetates *in situ* by substitution.[27]

Because heterogeneous reactions can pose difficulties when scaled, the dimerization of bromooctane was scaled from 2 mmol to 40 mmol (eqn (1)). The product was isolated in identical yield to the small-scale reaction (96% yield). This result demonstrates the potential of reductive dimerization for the synthesis of large quantities of material with a simple "mix and stir" procedure.

C_8H_{17}–Br $\xrightarrow[\text{1 equiv Mn} \atop \text{40 mL DMF, 40 °C, 24 h}]{\text{0.5 mol \% NiCl}_2\text{(glyme)} \atop \text{0.5 mol \% terpyridine } \mathbf{1}}$ 1/2 C_8H_{17}—C_8H_{17} (1)

40 mmol   96% yield, >4 g of product

Although we have not yet investigated the reaction mechanism, we believe that the product is eliminated from a dialkyl Ni[III] species formed from the net oxidative addition of an alkyl halide to an alkyl Ni[I] species. This proposal is in analogy to mechanistic hypotheses proposed for nickel-catalyzed homo-coupling of aryl halides,[28] and work on nickel-catalyzed couplings of organometallic reagents with alkyl halides.[20e,22]

While mechanistic questions remain, the nickel-catalyzed direct reductive coupling of alkyl halides, alkyl mesylates, alkyl

trifluoroacetates, or allylic acetates is a new, high-yielding alternative for the synthesis of dimeric molecules from convenient, bench-stable starting materials.

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