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Dimethylzinc-Initiated Radical Reactions

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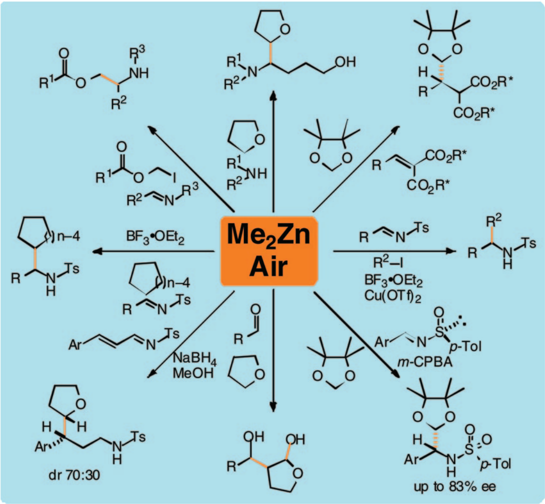
CONSPECTUS



Developments in modern organic synthesis owe much to the field of radical chemistry. Mild reaction conditions, high selectivity, good functional group tolerance and high product yield are features that have made reactions involving radical species indispensable tools for synthetic chemists. In part, the discovery of new radical initiators has led to the efficiency that now characterizes most radical reactions.

This Account describes our investigations of radical reactions initiated by dimethylzinc. In 2001, we unexpectedly observed this reaction while investigating the amidophosphane−copper-catalyzed asymmetric addition of dimethylzinc to *N*-sulfonyl imines with tetrahydrofuran (THF) as reaction solvent. However, instead of adding the desired methyl group to the *N*-sulfonyl imine, we produced the THF adduct in excellent yield. This result laid the foundation for our discovery of novel modes of reactivity. Further investigations of the unexpected addition reaction revealed that a trace amount of air was needed for reaction progress, indicating that radical intermediates were involved. Indeed, controlled injection of air into the reaction flask by a syringe pump through a sodium hydroxide tube afforded the products in good to excellent yield. In addition, the reaction proved to be chemoselective for a C═N bond over a C═O bond, as well as for 1,4-addition over 1,2-addition.

We developed asymmetric variants of the radical addition reaction of ethers to imines using chiral *N*-sulfinyl imines to produce the adducts in reasonably high stereoselectivity (up to 11:1). A 93:7 diastereomeric ratio of the adduct was obtained when bis(8-phenylmenthyl) benzylidenemalonate was used in the radical addition of ethers to C═C bonds. Interestingly, in the presence of dimethylzinc and air, arylamines, alkoxyamines, and dialkylhydrazines react with THF to give amino alcohols, oximes, and hydrazones, respectively, in moderate to high yields.

We performed a tin-free intermolecular addition of functionalized primary alkyl groups, generated from their corresponding iodides, to *N*-sulfonyl imines using dimethylzinc, air, boron trifluoride diethyl etherate, and a catalytic amount of copper(II) triflate. Direct C−H bond cleavage from cycloalkanes was also feasible in the presence of dimethylzinc, air, and boron trifluoride diethyl etherate to give the corresponding cycloalkyl radicals, which were suitable nucleophiles for *N*-sulfonyl imines. In all of the above reactions, dimethylzinc was a superior radical initiator than other conventional initiators such as dibenzoyl peroxide, diethylzinc, and triethylborane. We hope the coming decades will witness the report of other novel radical initiators that would complement the reactivity modes of existing ones.

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Introduction

The generation of radical species for the efficient construction of chemical bonds is a well-recognized strategy in organic synthesis.[1] This fact is exemplified by the numerous synthetic methods that have been reported to date. These methods usually require mild reaction conditions and have good functional group tolerance. As a result, they have been used in the stereoselective syntheses of simple and complex molecules. The present state-of-the-art of radical methods has its origin in the seminal work of Gomberg in 1900, who reported the isolation and reactivity of triphenylmethyl radical,[2] and that of Paneth in 1929, who reported the existence of alkyl radicals.[3] However, further research work in radical chemistry proceeded at a slow pace for almost 60 years, presumably due to the misconception that the high reactivity of radical species would preclude their selective reactions. Nevertheless, the mid-1980s marked the start of regular reports on radical chemistry based synthetic methods.

Radicals are generated through the homolytic cleavage of a bond by heat, light, or radiation. Examples of compounds that can serve as radical initiators include azo compounds, peroxides,[4] samarium iodide,[5] and organometallic compounds such as triethylborane[6] and hexabutylditin.[7] The choice of radical initiator and method used in producing the radical will depend on the reaction conditions and substrates utilized. Hence, advancements in radical chemistry have largely been driven by the development of new radical precursors.[1] The indium-mediated addition of alkyl radicals to glyoxylic hydrazones and phenyl vinyl sulfone reported by Naito,[8] the cyclization of α-haloamides to substituted pyrrolidinones by dimanganese decacarbonyl reported by Parsons,[9] and the stereoselective addition of alkyl iodides to chiral *N*-acylhydrazones by dimanganese decacarbonyl reported by Friestad[10] are recent examples. *In our opinion, the serendipitous discovery of a novel chemical reaction represents a major advancement in the field of chemical synthesis since such a reaction was not conceived by the human mind.* The body of this Account constitutes, in part, examples of such unplanned reactions that were discovered using dimethylzinc and air.[11]

Radical Addition of Ethers to Imines

We have reported the amidophosphane−copper-catalyzed asymmetric addition of diethylzinc to *N*-sulfonyl imines.[12] During further investigation, the attempted addition of dimethylzinc to the imine **1a** in the presence of the catalyst using THF as reaction solvent resulted in the addition of THF to **1a** to give adduct **2a** in high yield. A 3:2 diastereomeric mixture of **2a** was isolated in high yield when a solution of **1a** was treated with dimethylzinc (Scheme 1).[13] Notably, the methyl adduct was not isolated.

SCHEME 1. Addition of THF to **1a**

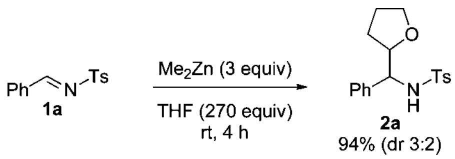
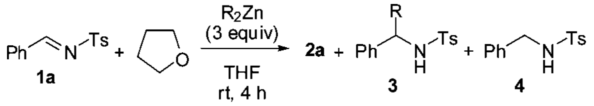


TABLE 1. Relationship of Organozinc-Initiated Addition of THF to **1a** with Bond Dissociation Energy



entry	R	R−H bde[a] (kJ /mol)	**2a** yield (%)	**3** yield (%)	**4** yield (%)
1	Me	440	94	0	0
2	Et	411	48	33	2
3	*i*-Pr	398	6	34	27
4	Ph	464	0	7	0

[a] bde = bond dissociation energy. The α-C−H bde of THF has been reported to be 385 kJ/mol in ref 16.

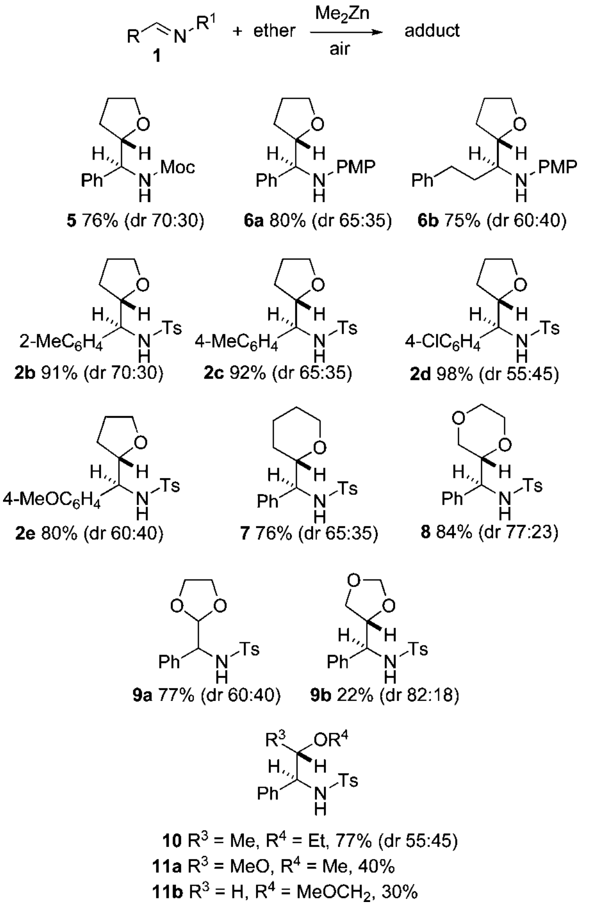
When the reaction was carried out under an argon atmosphere with silicone-greased apparatus joints, only 4% of **2a**, together with almost quantitative recovery of **1a**, was isolated after 2 days, thus, suggesting that air was required for reaction progress. A faster reaction of 1 h delivered **2a** in 95% yield as a result of constant bubbling of air (10 mL/h) into the reaction mixture. This result constituted the first example of using dialkylzinc for abstraction of a hydrogen atom to generate an α-alkoxyalkyl radical.[7,14,15]

Conventional radical initiators such as dibenzoyl peroxide and triethylborane produced a trace amount of **2a**. Almost quantitative recovery of **1a** resulted after 24 h in the former case, while 29% of ethyl adduct **3** (R = Et) was isolated in the latter. Furthermore, other organozinc reagents were found to be inefficient in the reaction, producing alkyl group adducts **3** (R = Et, *i*-Pr, or Ph) and reduced product **4** (Table 1).

It appears that the bde[16] of the R−H bond is related to the formation of **2a** using the corresponding diorganozinc. With the exception of entry 4, the bde is proportional to the yield of **2a**. This is presumably due to the higher hydrogen abstracting ability of the methyl radical relative to that of the ethyl radical, which in turn is more effective than the isopropyl radical. Phenyl radical might be too unstable to form from diphenylzinc.

Other N-substituted imines were found to be suitable for the production of the adducts (Scheme 2). Treatment of a solution of imines bearing an electron-withdrawing *N*-methoxycarbonyl or an electron-donating *N*-4-methoxyphenyl (PMP) in THF with dim-

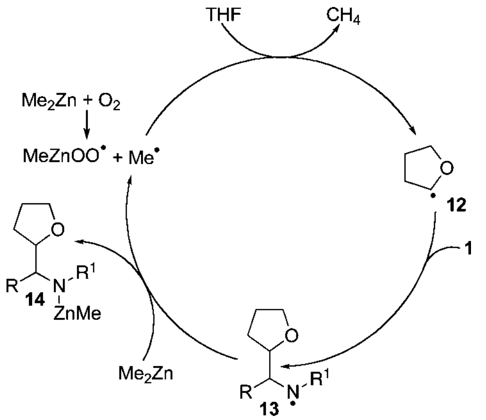
SCHEME 2. Dimethylzinc Initiated Addition of Ethers to Imines



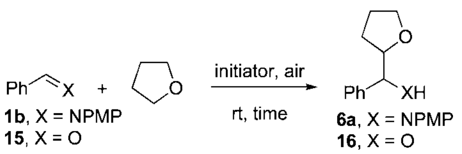
ethylzinc in the presence of air produced adducts **5**, **6a**, and **6b** in good yield. Substituted aromatic *N*-sulfonyl imines were applicable in the reaction to give the adducts **2b**–**2e** in good yield. Furthermore, other cyclic ethers such as tetrahydropyran (THP), 1,4-dioxane, and 1,3-dioxolane all produced their corresponding adducts **7**, **8**, and **9** in high yield. As expected, a regioselective addition was observed in the addition of 1,3-dioxolane to give regioisomers **9a** and **9b** in 7:2 ratio. This is presumably due to the higher stability and nucleophilicity of an α,α-dialkoxyalkyl radical relative to an α-alkoxyalkyl radical. Acyclic ethers were also suitable reactants. Diethyl ether produced the adduct **10** in good yield, while dimethoxymethane delivered a regioisomeric mixture of adducts **11a** and **11b** in 4:3 ratio. In these reactions, moderate diastereoselectivity was observed.

The formation of the adduct could be explained by a plausible mechanism which commences with the generation of methyl radical by the action of oxygen on dimethylzinc (Scheme 3).[17] The resulting methyl radical then abstracts an α-hydrogen of THF to produce tetrahydrofuran-2-yl radical (**12**), which adds to imine **1** to give aminyl radical **13**. Subsequent reaction of dimethylzinc with **13** generates a methyl radical (as the reaction chain carrier) and zinc amide **14**, which upon workup affords the product. The direct abstraction of a hydrogen atom by **13** from THF might be a minor pathway since an excess amount of dimethylzinc is required for complete consumption of starting material.

SCHEME 3. Plausible Mechanistic Rationale for Addition of THF to Imine **1**



SCHEME 4. Initiator Controlled Chemoselective Addition of THF Radical to Imine **1b** and **15**



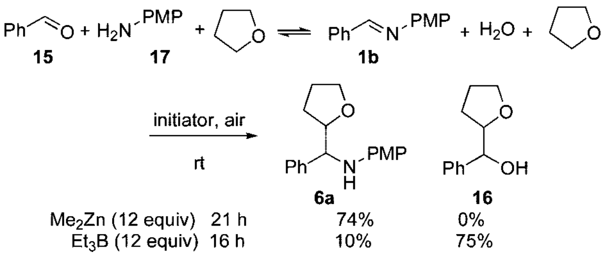
1b/15	initiator (equiv)	time (h)	product	yield (%)
1b	Me_2Zn (6)	5	6a	83
1b	Et_3B (12)	18	6a	63
15	Me_2Zn (12)	120	16	<8
15	Et_3B (12)	6	16	81

Initiator Controlled Chemoselective Addition of Ether Radicals to Imines and Aldehydes

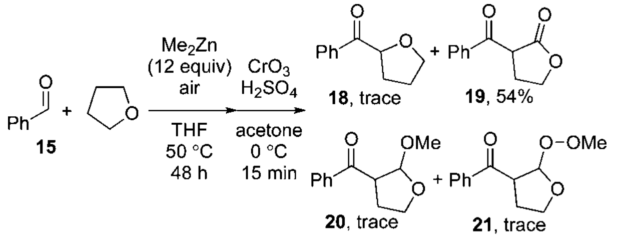
One of the hallmarks of an efficient synthetic method is its selectivity for a particular reaction site within a given set of potential reaction sites in a molecule. Sometimes, in radical reactions, this chemoselectivity is governed by the radical initiator used when the initiator also works as a mediator.[18] Separate solutions of benzaldehyde *N*-PMP imine (**1b**) and benzaldehyde (**15**) in THF were treated with dimethylzinc in the presence of air (Scheme 4).[19] Interestingly, only 8% of the expected adduct was isolated after 5 days when **15** was used, whereas a good yield of the expected adduct was obtained when **1b** was used. Both reactions proceeded when triethylborane initiator was used.[20]

Further supportive results were obtained when a three-component mixture of **15**, *p*-anisidine (**17**), and THF was separately treated with dimethylzinc and triethylborane in the

SCHEME 5. Initiator-Controlled Chemoselective Addition of THF Radical to an Equilibrium Mixture of **15** and **17**



SCHEME 6. Reaction of Aldehyde **15** with THF Radical Generated by Dimethylzinc and Subsequent Jones Oxidation



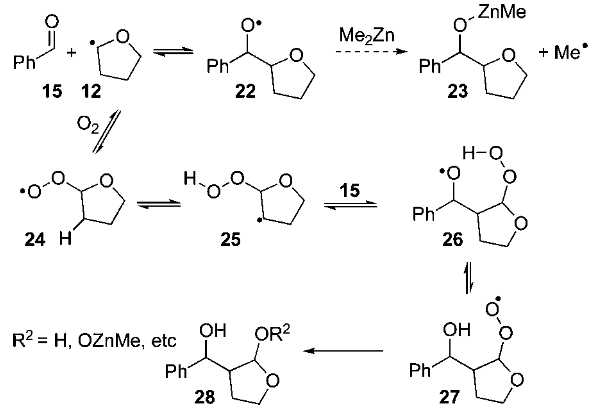
presence of air (Scheme 5). Dimethylzinc promoted the selective addition of the THF-2-yl radical to C=N bond, while triethylborane promoted selective addition to C=O bond.

Dimethylzinc-Mediated Reaction of Aldehydes with the *β*-Carbon of an Oxygenated THF

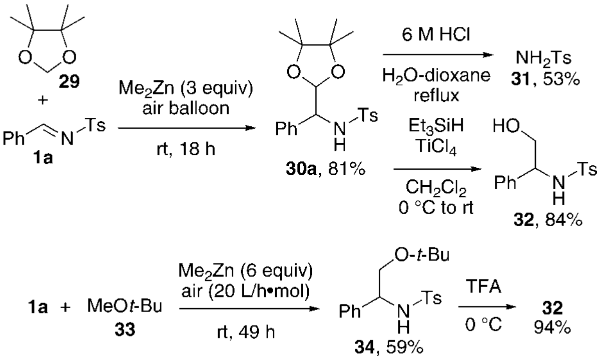
During the investigation in the chemoselective addition of ether radicals to imines and aldehydes, we found an unexpected reaction (Scheme 6).[21] Portionwise (3 equiv each) addition of dimethylzinc (12 equiv) to a solution of aldehyde **15** in THF at 50 °C followed by Jones oxidation of the crude mixture afforded *β*-keto ester **19** along with trace amounts of ketone **18**, *β*-keto acetal **20**, and *β*-keto peroxide **21**.

The portionwise addition of dimethylzinc, as well as elevated temperature, was essential to the production of **19** since a single addition of dimethylzinc at room temperature resulted in the formation of **18** (10%), **19** (10%), **20** (8%), and **21** (17%) after Jones oxidation. A plausible mechanism for the formation of **19** is detailed in Scheme 7. The THF-2-yl radical (**12**) adds to **15** to give unstable alkoxyl radical **22**, which reverts back to **12** and **15** in the absence of an efficient alkoxyl radical trapper, such as triethylborane. Subsequent reaction of **12** with oxygen would generate peroxyl radical **24**, which in turn undergoes an intramolecular 1,4-hydrogen abstraction[22] to give 2-hydroperoxy-THF-3-yl radical (**25**). Following addition of **25** to **15** gives alkoxyl radical **26**, which undergoes an intramolecular hydrogen transfer to give relatively stable peroxyl radical **27** (bde HO–H 498 kJ/mol vs HOO–H 365 kJ/mol),[16] which is an intermediate for the precursors of the observed products.

SCHEME 7. Plausible Mechanism for the Generation of an α-Oxygenated THF *β*-Radical **25** and Formation of **28**



SCHEME 8. Installation of Functionalized One-Carbon Unit to Imine **1a**

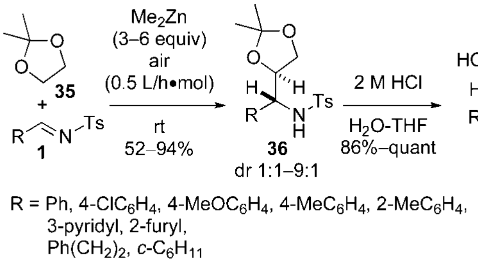


Addition of Functionalized Carbon Units to *N*-Sulfonyl Imines

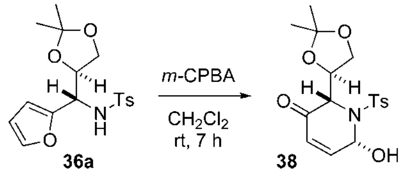
Given the success of our dimethylzinc-mediated addition of ethers to imines,[13] we then sought to apply this method to the addition of functionalized ethers, which have easily manipulable moieties.[23] To this end, the reactions of imine **1a** with 4,4,5,5-tetramethyl-1,3-dioxolane (**29**) and *tert*-butyl methyl ether (**33**) produced the desired adducts **30a** and **34**, respectively (Scheme 8).

Several attempts to cleave the acetal moiety of **30a** under standard acidic conditions failed. Indeed, reaction of **30a** in a refluxing mixture of dioxane and water gave tosylamide **31**, probably via cleavage of the benzylic C–N bond. However, reductive cleavage of the acetal group was achieved using titanium tetrachloride and triethylsilane to give synthetically useful amino alcohol **32**.[24] Also, the *tert*-butyl group of **34** was removed with trifluoroacetic acid (TFA) to give **32** in high yield. Hence the introduction of a functionalized one-carbon unit to the imine was accomplished. The introduction of a

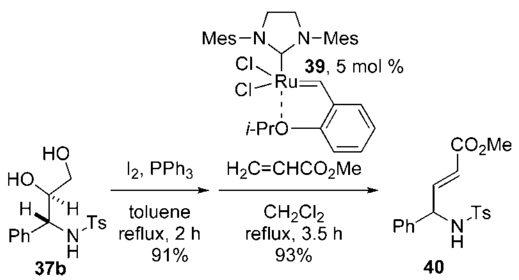
SCHEME 9. Installation of Functionalized Two-Carbon Unit to Imines



SCHEME 10. Aza-Achmatowich Rearrangement of Furan **36a** to Dihydropyridone **38**



SCHEME 11. Transformation of Diol **37b** into Alkene **40**



functionalized two-carbon chain to *N*-sulfonyl imines **1**, derived from aromatic and aliphatic aldehydes, was achieved in high yield with essentially moderate diastereoselectivity using 2,2-dimethyl-1,3-dioxolane (**35**) followed by acidic cleavage of the adducts **36** to give vicinal diol **37** in high yield (Scheme 9).

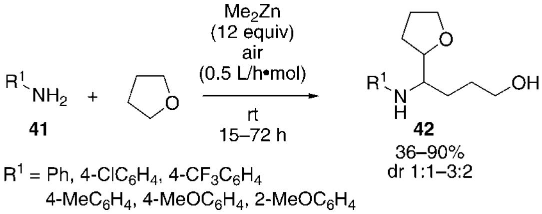
The utility of the adduct was demonstrated by conversion of adduct **36a** into dihydropyridone **38**,[25] a precursor of amino sugars,[26] by the aza-Achmatowich rearrangement (Scheme 10).

Furthermore, alkene **40** was synthesized from 1,2-diol **37b** (Scheme 11). This synthetic sequence constitutes the introduction of a functionalized three-carbon chain.

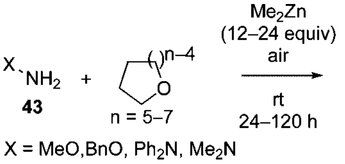
Radical Reaction of Cyclic Ethers with Arylamines, Alkoxyamines, and Dialkylhydrazines

During our investigation on the three-component reaction of aldehyde **15**, aniline (**41a**), and THF in the presence of dimethylzinc and air, alcohol **42** (R^1 = Ph) was isolated in 26% yield. Further investigation in the absence of **15** gave **42** (R^1 = Ph) in high yield (Scheme 12).[27]

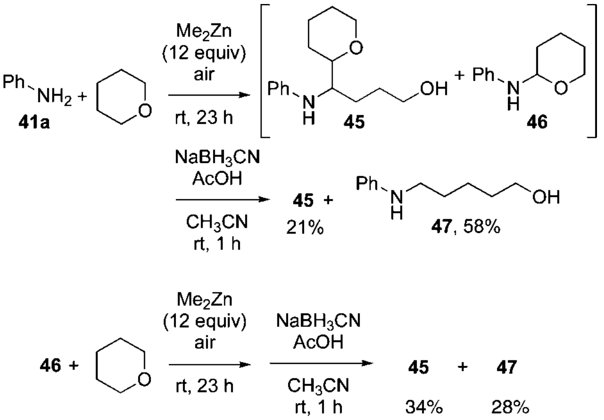
SCHEME 12. Reaction of Amine **41** with THF in the Presence of Dimethylzinc



SCHEME 13. Reaction of Alkoxyamines and Hydrazines with Cyclic Ethers



SCHEME 14. Reaction of THP with **41a**

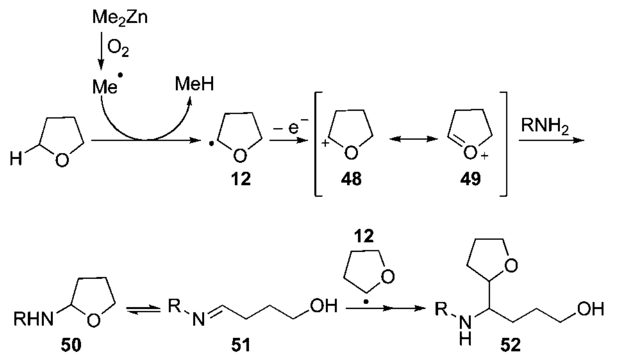


Amines bearing electron-withdrawing and electron-donating groups were compatible with the reaction conditions. Dimethylzinc proved superior to both diethylzinc and triethylborane. Product **42** (R^1 = Ph) was obtained in 37% yield after 75 h with the use of diethylzinc, while triethylborane produced **42** (R^1 = Ph) in 17% yield after 48 h.

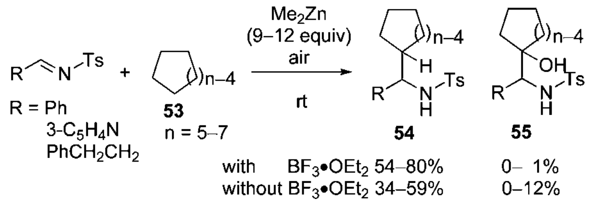
Alkoxyamines and dialkylhydrazines were also applicable in the reaction to give oximes and hydrazones, respectively (Scheme 13).

The involvement of an aminal intermediate in the reaction mechanism was confirmed by the reaction of amine **41a** and THP (Scheme 14). Exposure of a solution of **41a** in THP to dimethylzinc and air produced a mixture of amino alcohol **45** and aminal **46**, which was subsequently treated with sodium cyanoborohydride to afford **45** and **47**. Application of a similar reaction sequence to a solution of **46** in THP produced **45** and **47**. Thus, a plausible mechanism for the formation of **42** and **44** is shown in Scheme 15.

SCHEME 15. Proposed Mechanism for the Reaction of Amines with Ethers



SCHEME 16. Aminoalkylation of Cycloalkanes



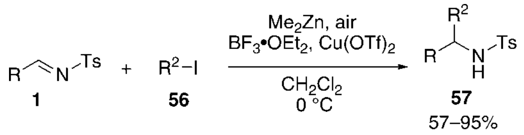
THF-2-yl radical (**12**), generated by the action of methyl radical on THF, undergoes further oxidation, probably with molecular oxygen, to give α-alkoxyalkyl cation **48**[28] stabilized by resonance form **49**, which is attacked by the amine to give aminal **50**. Provided the electron-donating power of nitrogen is high enough, the production of imine **51** becomes favored. Subsequent addition of **12** to **51** affords **52** after workup.

Direct Aminoalkylation of Cycloalkanes

The selective abstraction of a hydrogen atom from the α-carbon of an ether molecule by a methyl radical is a thermodynamically favored step.[16] Also favorable, albeit to a lesser extent, should be the abstraction of a hydrogen atom from cyclohexane (bde Me–H 440 kJ/mol vs cyclohexyl–H 400 kJ/mol).[16] Indeed, cycloalkyl radicals, generated from their corresponding cycloalkanes by dimethylzinc–air, were added to *N*-sulfonyl imines (Scheme 16).[29]

Interestingly, in all cases, boron trifluoride diethyl etherate suppressed the formation of oxidized product **55** to give higher yields of adduct **54**. Furthermore, both diethylzinc and triethylborane were less efficient initiators than dimethylzinc. Adduct **54** was produced in 26% yield along with the ethyl adduct **3** (R = Et) (44% yield) and reduced product **4** (11% yield) when diethylzinc was used. The use of triethylborane produced adduct **54** in 22% yield along with 44% of the ethyl adduct **3** (R = Et).

SCHEME 17. Alkylation of *N*-Sulfonyl Imines **1** with Alkyl Iodides



R = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4,
1-Naph, 2-Naph, $Ph(CH_2)_2$, *c*-C_6H_{11}
R^2 = Bu, *i*-Pr, *c*-C_6H_{11}, $AcO(CH_2)_4$, $Cl(CH_2)_4$, $Cl(CH_2)_3$

Intermolecular Addition of Primary Alkyl Radicals in the Absence of Tin

Despite the versatility of trialkyltin hydrides in organic synthesis, the development of tin-free methods for the generation of radical species is an important challenge in organic synthesis due to the toxicity of tin compounds. Thus, synthetic endeavors to develop tin-free synthetic methods have been reported.[11,30,31] Continued investigations using our dimethylzinc–air method revealed that tin-free radical addition of functionalized alkyl groups to *N*-sulfonyl imines is possible in the presence of dimethylzinc (Scheme 17).[32] Longer reaction time, as well as reduced yield were observed in the absence of boron trifluoride diethyl etherate and/or copper(II) triflate.

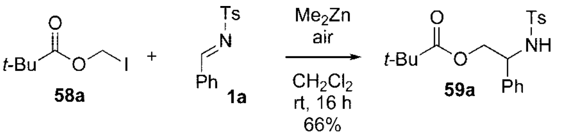
Replacing dimethylzinc with diethylzinc[14] when hexyl iodide was used resulted in isolation of hexyl adduct **57** (R = Ph, R^2 = hexyl) in 11% yield along with the ethyl adduct **3** (R = Et) in 82% yield. The use of triethylborane was equally inefficient giving hexyl adduct **57** (R = Ph, R^2 = hexyl) in less than 14% yield and the ethyl adduct **3** (R = Et) in 32% yield.

Addition of Acyloxymethyl to Imines

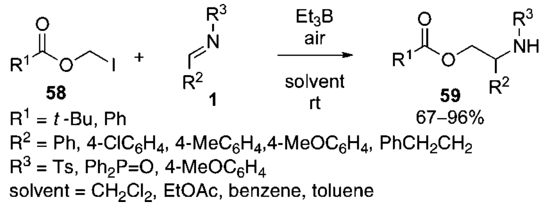
An α-acyloxyalkyl radical is presumably a stabilized nucleophilic radical and hence equivalent to an α-alkoxycarbanion, whose generation usually involves tin–lithium[33] or magnesium–halogen[34] exchange reactions, which require strongly basic and strictly anhydrous deoxygenated conditions and low temperature. Given these drawbacks, the generation of acyloxyalkyl radicals with mild and flexible methods is advantageous, though toxic tin compounds have been utilized for this purpose.[35,36] Hence we investigated a new tin-free method for generation of α-acyloxyalkyl radical.[37] Adduct **59a** was obtained after treatment of imine **1a** with iodomethyl pivalate (**58a**) in the presence of dimethylzinc and air (Scheme 18).

Although the desired radical addition failed when diethylzinc was used, to give instead the ethyl adduct **3** (R = Et) (76%) and reduced product **4** (9%), the use of triethylborane facilitated the reaction to give adduct **59a** in excellent yield (Scheme 19).

SCHEME 18. Dimethylzinc-Initiated Addition of Acyloxymethyl Radicals to Imine **1a**



SCHEME 19. Et$_3$B-Mediated Addition of Acyloxymethyl to Imines



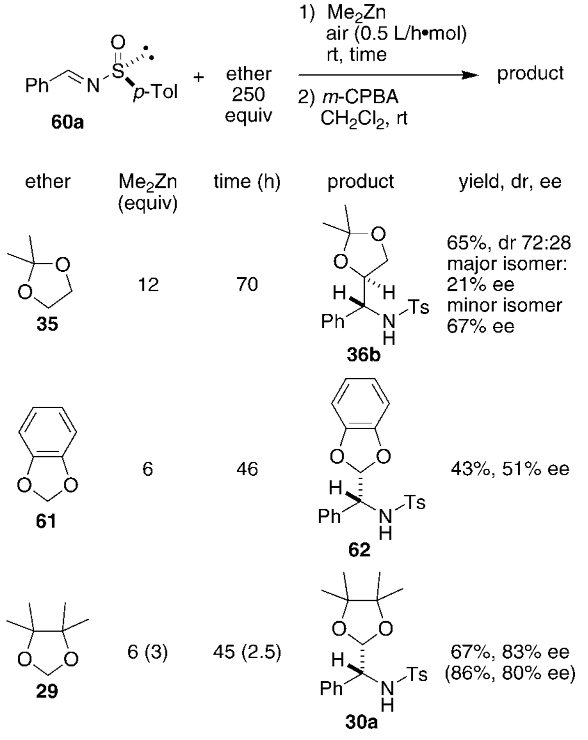
Iodomethyl benzoate (**58**, R^1 = Ph) was also a suitable radical source. *N*-PMP and *N*-diphenylphosphinoyl imines were also applicable. Interestingly, *N*-PMP imines reacted faster than the more electron-deficient *N*-tosyl imines. Dichloromethane, ethyl acetate, benzene, and toluene were all good reaction solvents.

Asymmetric Addition of Ethers to *N*-Sulfinyl Imines

The use of chiral *N*-sulfinyl imines, pioneered independently by Davis and Ellman, for synthesis of enantiomerically enriched amine compounds is well documented.[38] This is due to their ease of synthesis, good reactivity, and predictable stereochemical preference. However, with the exception of a pinacol-type coupling reported by Lin, Xu, and co-workers,[39] there has been no report of addition of radical species onto *N*-sulfinyl imines. To gain insight into this relatively unexplored area, we decided to deploy chiral *N*-sulfinyl imines to develop an asymmetric variant of our reaction. Separate solutions of *N*-sulfinyl imine **60a** in 2,2-dimethyl-1,3-dioxolane (**35**), 1,3-benzodioxole (**61**), and 4,4,5,5-tetramethyl-1,3-dioxolane (**29**) were treated with dimethylzinc and air to give enantiomerically enriched sulfonamide adducts after oxidation of the crude mixture from the radical addition step (Scheme 20).[24]

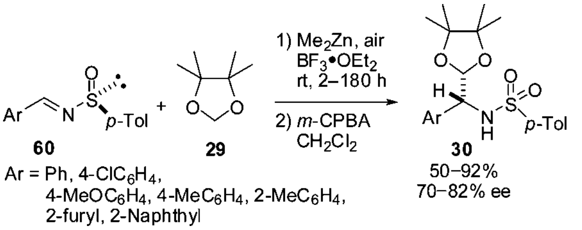
The reaction with **35** required more equivalents of dimethylzinc and longer reaction time than the reaction involving **61** and **29**. This is presumably due to the higher reactivity of an α,α-dialkoxyalkyl radical relative to an α-alkoxyalkyl radical. The higher enantiocontrol observed with **29** relative to that observed with **61** is probably due to the bulkiness of **29**. Unfortunately, a complex mixture of products was obtained when (*R*)-*N*-*tert*-butanesulfinyl benzaldehyde imine, which sometimes gives better results than **60a**,[38] was employed in the reaction with **29**. Further investigations revealed that the reaction with **29** could be accelerated using boron trifluoride diethyl etherate to give adduct **30a** in higher yield with comparable enantioselectivity (Scheme 20). Aromatic sulfinyl imines **60** bearing an electron-withdrawing or an electron-donating group were suitable substrates in the reaction (Scheme 21). The desired adducts **30** could also be produced from both polyaromatic and heteroaromatic substrates.

SCHEME 20. Asymmetric Radical Addition of Ethers to Imine **60a**[a]



[a] Number in parentheses indicates values obtained when boron trifluoride diethyl etherate (1 equiv) was used.

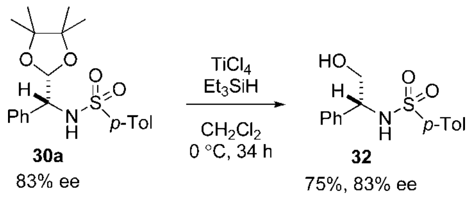
SCHEME 21. Asymmetric Radical Addition of **29** to Imines **60**



The chiral sulfonamide **30a** was converted into useful known chiral amino alcohol **32**[40] without loss of optical purity, using a Lewis acid promoted reductive cleavage strategy, and the absolute configuration of the adduct was determined as shown in the scheme (Scheme 22).

The model in Figure 1 explains the origin of the stereocontrol observed in the reaction. There is a bias for *si*-face attack between the diastereotopic faces of the *N*-sulfinyl imine as a consequence of the *re*-face location of the bulky tolyl group.[41]

SCHEME 22. Transformation of **30a** into Alcohol **32**



Conjugate Addition of THF-2-yl to α,*β*-Unsaturated *N*-Sulfonyl Imines

During initial investigations of additions of THF to 2-napthaldehyde *N*-sulfonyl imine **1c**, we observed addition of the ether radical onto the naphthyl ring to give adduct **64** along with expected adduct **63** (Scheme 23).

While the isolation of adduct **64** was somewhat undesired, it provided the inspiration to deploy α,*β*-unsaturated *N*-sulfonyl imines in the radical addition reaction. Thus, treatment of a solution of cinnamaldehyde *N*-tosyl imine (**65a**) in THF with dimethylzinc was performed.[42] Subsequent hydrolysis of the resulting crude mixture with acid followed by reduction gave alcohol **66**, 1,2-adduct **67a**, and diene **68** (Scheme 24). Encouraged by these results, further experimentation revealed that the product distribution could be directed toward the desired product by slowly adding a solution of **65a** in THF to a solution of dimethylzinc in THF.

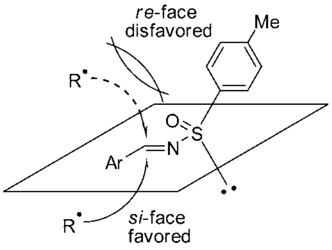
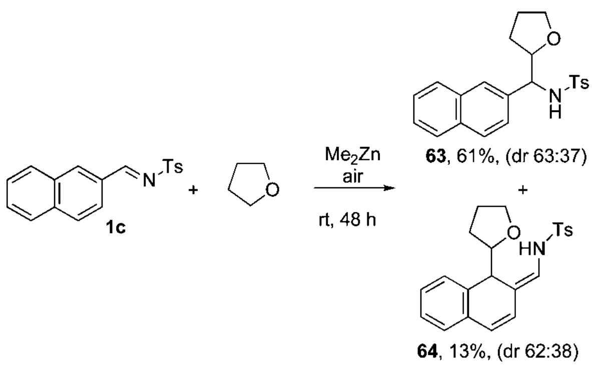
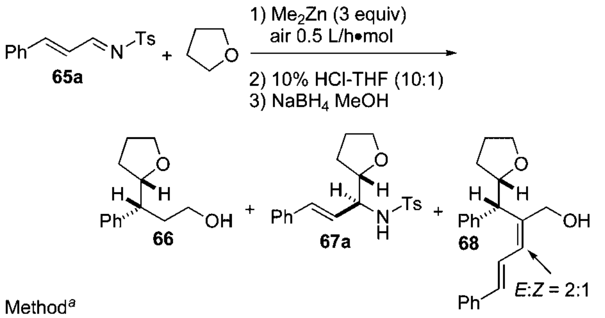


FIGURE 1. Rationale of stereochemical outcome.

SCHEME 23. Addition of THF Radical to Imine **1c**



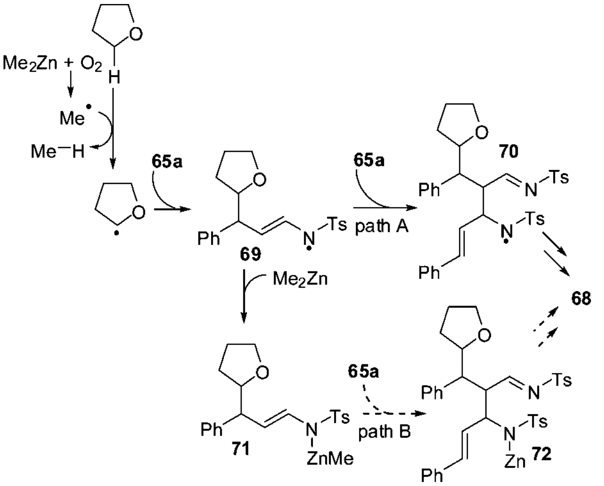
SCHEME 24. Selective 1,4-Addition of THF to Imine **65a**[a]



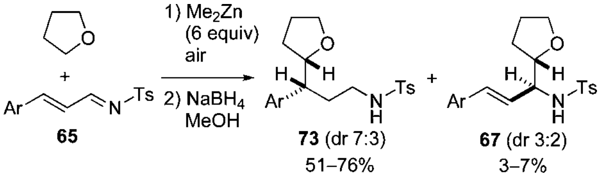
Method[a]	66	67a	68
A	24% (dr = 7:3)	3% (dr = 3:2)	35% (dr = 7:3)
B	68% (dr = 7:3)	3% (dr = 3:2)	3% (dr = 7:3)

[a] For method A, Me_2Zn was added to a THF solution of **65a** within 1 min. For method B, a THF solution of **65a** was added to a solution of Me_2Zn in THF over 6 h.

SCHEME 25. Proposed Mechanism for the Formation of Diene **68**



SCHEME 26. Selective 1,4-Addition of THF to Imine **65**



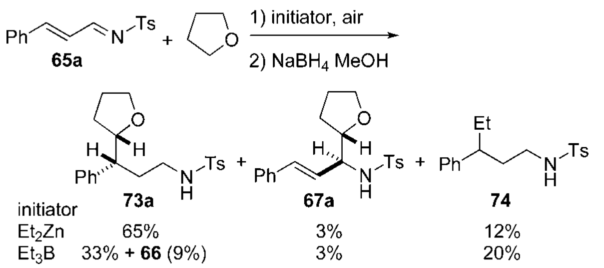
Ar = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 2-MeC_6H_4, 4-ClC_6H_4, 2-Naphthyl

A plausible mechanism for product formation is illustrated in Scheme 25. In the presence of a high concentration of **65a**, aminyl radical **69** would favor path A to give aminyl radical **70**, which is converted into **68** probably via **72**. However, a low concentration of **65a** would facilitate the formation of zinc enamide **71**, which would react with **65a** (path B) to give zinc amide **72**. The decreased formation of **68** in the slow addition procedure indicates that path A is the dominant path by which **68** is formed since path B would have led to formation of **68** in a comparable yield, albeit at a slower rate than path A.

With the optimized conditions in hand, other substrates **65** were deployed in the radical addition reaction to predominantly give the desired conjugate product **73** (Scheme 26).

The use of diethylzinc or triethylborane in place of dimethylzinc gave less efficient results (Scheme 27). In both

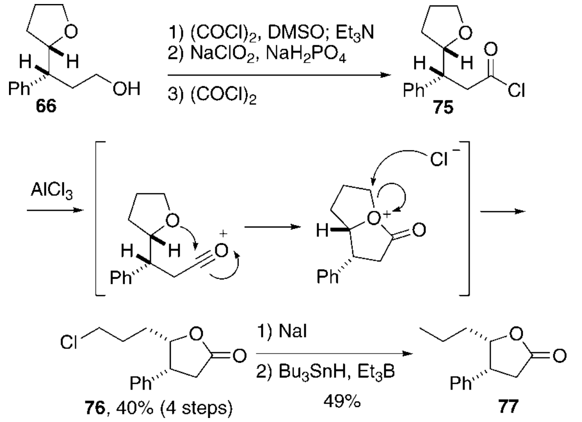
SCHEME 27. Et$_2$Zn- and Et$_3$B-Mediated Addition of THF to Imine **65a**[a]



initiator	73a	67a	74
Et$_2$Zn	65%	3%	12%
Et$_3$B	33% + **66** (9%)	3%	20%

[a] The diastereomeric ratios of **73a** and **67a** were identical to those observed in the reaction with Me$_2$Zn.

SCHEME 28. Transformation of Major Isomer of **66** into Lactones **76** and **77**



instances, competitive ethyl radical addition led to the formation of ethyl adduct **74**.

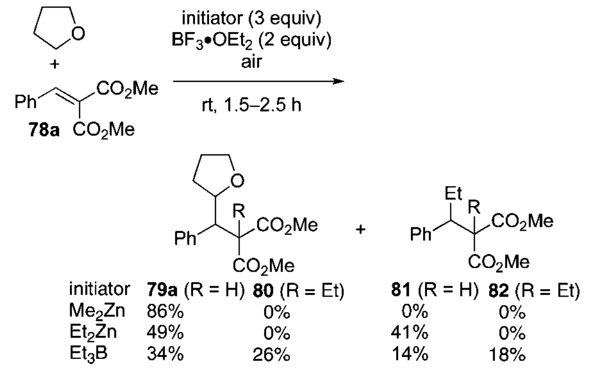
The utility of the obtained adduct was demonstrated by conversion of adduct **66** into known lactone **77**[43] thus establishing the relative stereochemistry of adduct **66** (Scheme 28). Acylative tetrahydrofuran ring opening[44] of **75**, obtained from **66**, produced lactone **76**. Subsequent dehalogenation of **76** gave **77**. In essence, the THF moiety of the adduct had been converted into an α,ω-functionalized four-carbon chain.

Conjugate Addition of Ethers to Alkylidenemalonates

To widen the scope of our dimethylzinc radical addition reaction, we envisioned the use of alkylidenemalonates as radical acceptors (Scheme 29).[45]

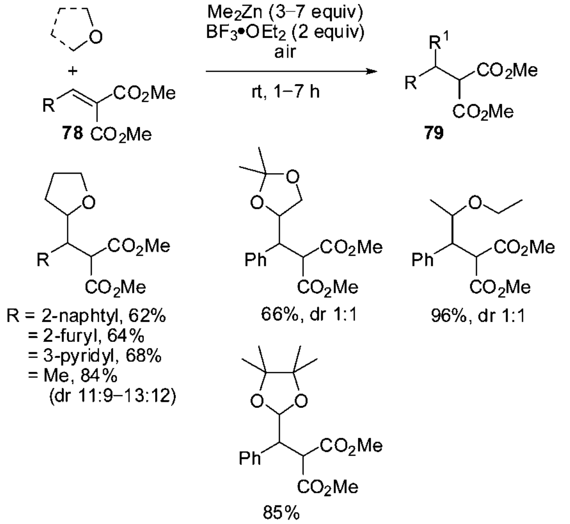
In the reaction involving dimethyl 2-benzylidenemalonate **78a**, dimethylzinc proved to be a better radical initiator than diethylzinc or triethylborane since byproducts **80**−**82** were formed in the latter two cases. Furthermore, boron trifluoride diethyl etherate facilitated the THF radical addition to give adduct **79a** in high yield. Alkylidenemalonates bearing naphthyl, furyl, pyridyl, and methyl groups were applicable in the reaction to give the adducts in good yields (Scheme 30). In addition, diethyl ether and dioxolane **29** and **35** were all suitable ethers for the radical conjugate reactions giving the desired adducts in good yields.

SCHEME 29. Addition of THF Radical to Alkylidenemalonate **78a**



initiator	79a (R = H)	80 (R = Et)	81 (R = H)	82 (R = Et)
Me$_2$Zn	86%	0%	0%	0%
Et$_2$Zn	49%	0%	41%	0%
Et$_3$B	34%	26%	14%	18%

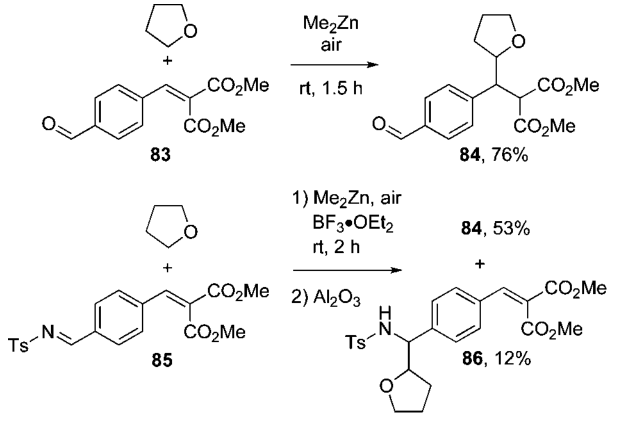
SCHEME 30. Addition of Other Ethers to Other Alkylidenemalonates



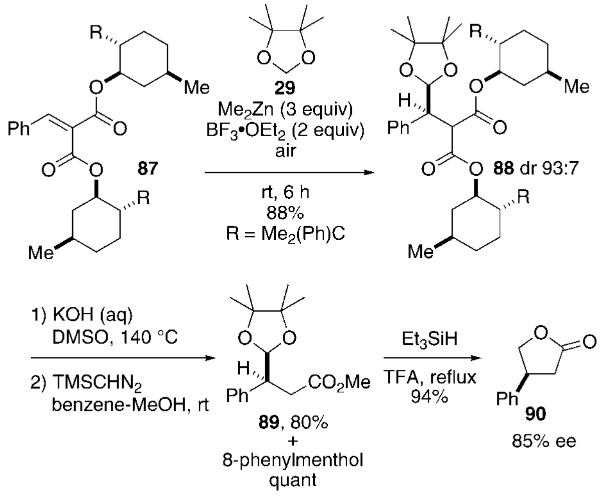
A chemoselective addition of the THF-2-yl radical was observed (Scheme 31). The THF-2-yl radical added preferentially in a conjugate manner to the C═C bond of malonate **83** to give adduct **84** in good yield without addition to the C═O bond. Moreover, addition to the C═C bond of malonate **85** preferentially took place, although addition to the C═N bond was also observed, to give **84** and adduct **86** in an 82:18 ratio after hydrolysis of the crude mixture on an alumina column. These results indicate that a Michael acceptor is more reactive than an imine, which in turn is more reactive that an aldehyde.

The use of chiral bis(8-phenylmenthyl) benzylidenemalonate (**87**) and **29** allowed for the synthesis of chiral adduct **88** with good diastereoselectivity (Scheme 32). Subsequent saponification of the ester group along with decarboxylation gave methyl ester **89** after esterification of the resultant carboxylic acid. Notably, the chiral auxiliary, 8-phenylmenthol[46]

SCHEME 31. Chemoselective Radical Conjugate Addition of THF to Aldehyde **83** and Imine **85**



SCHEME 32. Asymmetric Addition to 8-Phenylmenthyl Benzylidenemalonate and Conversion of the Adduct into Enantiomerically Enriched Lactone **90**



was recovered quantitatively. Reduction of **89** gave lactone **90**[47] in high yield and good ee.

Conclusion

Over the last 6 years, we have reported the use of dimethylzinc in conjunction with air as an efficient radical initiator, which complements the reactivity modes of other radical initiators. Notably, the capability of this method has been tested in direct C—H activation of ethers and cycloalkanes to generate carbon-centered radicals, which chemoselectively added to imines to afford the adducts in high yield with high enantiocontrol. Furthermore, a tin-free method for the generation of primary alkyl radicals was equally feasible with the dimethylzinc—air method. The mild reaction conditions, use of relatively less toxic reagents, high selectivity, and essentially good product yield make dimethylzinc a synthetically useful radical initiator with much potential for unprecedented reaction modes. Of note is the potential of dimethylzinc to generate nonoxygenated carbon-centered radicals. Indeed, there is ongoing research effort in our laboratory focused on the discovery of new reaction modes of dimethylzinc.

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BIOGRAPHICAL INFORMATION

Tito Akindele obtained a B.Sc. Chem/USA honors degree in Chemistry from the University of Leicester, U.K., in 2000 with a year stint at The State University of New York at Buffalo as an exchange student. In 2004, he was awarded a Ph.D. degree from the University of Leeds, U.K., under the supervision of Doctor Stephen P. Marsden. He joined Fujifilm Imaging Colorants in Manchester, U.K. following a postdoctoral stay with Professor Kiyoshi Tomioka at Kyoto University, Japan. He will be moving to Pfizer in Sandwich, U.K. in January 2009. His research interests encompass development of novel asymmetric synthetic methods for the synthesis of biologically active compounds.

Ken-ichi Yamada was born in 1973 in Tokyo, Japan. He completed his Ph.D. under the supervision of Professor Masakatsu Shibasaki in 2001 (University of Tokyo, Japan). He joined Kyoto University as an Assistant Professor in 2001 and has worked in the laboratory of Professor Kiyoshi Tomioka since then. He was promoted to Associate Professor in 2006. He received the Pharmaceutical Society of Japan Award for Young Scientists in 2007. His research interests are in synthetic organic chemistry, asymmetric synthesis, and organometallic chemistry.

Kiyoshi Tomioka, born in 1948 in Tokyo, Japan, is a Professor of the Graduate School of Pharmaceutical Sciences, Kyoto University. He received his Ph.D. from the University of Tokyo in 1976 under the direction of Professor S. Yamada. He worked as a postdoctoral fellow with Professor. A. I. Meyers at Colorado State University in 1976—1978. He joined the University of Tokyo as a Research Associate in 1978 and was promoted to Associate Professor in 1983. He moved to Osaka University as a Professor in 1992. He has been a Professor at Kyoto University since 1996. He received The Pharmaceutical Society of Japan Award in 2003. His research interests are in synthetic organic chemistry, asymmetric synthesis, organometallic chemistry, and molecular architecture.

FOOTNOTES

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