Pure & Appl. Chem., Vol. 71, No. 2, pp. 239–245, 1999.
Printed in Great Britain.
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Designer Lewis acid catalysts for selective organic synthesis*

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Abstract: The present paper covers the progress in stereo-, regio-, and chemoselective carbon-carbon bond-forming reactions promoted by structurally well-designed aluminum aryloxides. Compared with conventional Lewis acids, these aluminum reagents strongly coordinate with various oxygen-containing substrates, and the coordination aptitude is strongly affected by the steric environment of the metal ligands. In principle, the carbonyl groups of the bound substrates are electronically activated but sterically deactivated depending on the aluminum reagent and the type of the reaction employed. This review specifically highlights the selective organic reactions using ATPH.

INTRODUCTION

Great progress has been made in Lewis acid-promoted carbon–carbon bond-forming reactions in organic synthesis. Traditionally, the Friedel–Crafts reaction [1], ene reaction [2], Diels–Alder reaction [3], and Mukaiyama aldol synthesis [4] are catalyzed by ordinary Lewis acids such as $AlCl_3$, $TiCl_4$, BF_3 and $SnCl_4$. These conventional Lewis acids in solution exist as dimeric, trimeric, or higher oligomeric structures, and can activate various functional groups of organic substrates. Unfortunately, the reactions usually proceed efficiently, albeit with low stereo-, regio-, and chemoselectivities. In contrast, relatively simple modification of the ligands of conventional Lewis acids leads to monomeric Lewis acids in organic solvent and consequently to high Lewis-acidity and reactivity. Furthermore, upon coordination with designed ligand(s), the Lewis acid exhibits new selectivity. As a contribution from our laboratory, several designer aluminum reagents including methylaluminum bis(2,6-di-*tert*-butyl-4methylphenoxide) (MAD) [5] and aluminum tris(2,6-diphenylphenoxide) (ATPH) [6] were readily prepared from the corresponding bulky phenol and Me_3Al (Fig. 1), and demonstrated to be potentially useful for directing chemical transformations. Lewis-acidity of these reagents might attenuate with the coordination of more electron-donating aryloxides, but this can be compensated for by loosening of the aggregation. Compared with conventional Lewis acids, the steric effect of designer aluminum reagents have found of great significance in selective organic synthesis which is the subject of this article.

STRUCTURAL FEATURES OF ATPH

The X-ray crystal structure of the N,N-dimethylformamide(DMF)-ATPH complex [7] disclosed that the three arene rings of ATPH form a propeller-like arrangement around the aluminum center, and hence ATPH has a cavity with C_3 symmetry. By contrast, the X-ray crystal structure of the benzaldehyde-ATPH complex [7] shows that the cavity surrounds the carbonyl substrate with slight distortion from the C_3 symmetry. Particularly notable structural feature of these aluminum-carbonyl complexes is the Al-O-C angles and Al-O distances, which clarify that the size and the shape of the cavity changes flexibly depending on the substrates. According to these models, the cavity should be able to differentiate carbonyl substrates, which, when encapsulated into the cavity, should exhibit abnormal reactivity under

*Lecture presented at the 9th International Symposium on Novel Aromatic Compounds (ISNA-9), Hong Kong, China, 2–7 August 1998, pp. 209–302.
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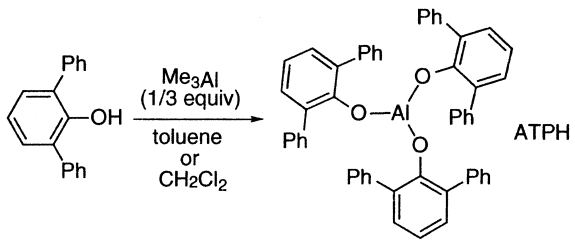

Fig. 1 Preparation of ATPH.

the steric and electronic environment of the arene rings. ^{1}H-NMR measurement of crotonaldehyde-ATPH complex (300 MHz, CD_2Cl_2) revealed that the original chemical shifts of the aldehydic proton (H_a) at δ 9.50, and the α-and β-carbon protons (H_b and H_c) at δ 6.13 and δ 6.89, were significantly shifted upfield to δ 6.21, δ 4.92 and δ 6.40, respectively. The largest Δδ value of H_a of 3.29 p.p.m. suggests that the carbonyl is effectively shielded by the arene rings of the cavity. This observation is in contrast to the resonance frequencies of the crotonaldehyde-Et_2AlCl complex at –60 °C (H_a: δ 9.32; H_b: δ 6.65; H_c: δ 7.84), and those of crotonaldehyde complexes with conventional Lewis acids [8].

MOLECULAR RECOGNITION WITH BULKY ALUMINUM REAGENTS: DISCRIMINATION OF TWO DIFFERENT ALDEHYDES

The monomeric aluminum phenoxides have sufficient Lewis-acidity and thus bind with polar functionalities. The complexation is heavily depends on the structural features of these functional groups. Thus, functional groups on the outside of a molecule bind to bulky aluminum reagents rather tightly, and functional groups on the inside of a molecule could not form stable complexes. In other words, the steric bulk of aluminum reagents appears to play a crucial role in discriminating among structurally or electronically similar substrates. For example, ATPH can discriminate between structural difference of aldehydes possessing similar reactivity, thereby facilitating the selective functionalization of the less hindered aldehyde carbonyl [9,10]. It should be noted that the complexed aldehyde could only react with nucleophiles. The reaction gave relatively low chemoselectivity with other typical Lewis acids. This fact emphasizes that the cavity of ATPH plays an important role in differentiating between the reactivities of the two different aldehydes. Obviously, the coordinated aldehyde is electronically activated but sterically deactivated with bulky aluminum reagents. The selective functionalization of more sterically hindered aldehydes was accomplished by the combined use of MAPH and organolithiums (RLi; R = *n*-Bu or Ph) [11]. In this system, MAPH acted as a carbonyl protector of a less hindered aldehyde and therefore the carboanions preferentially react with more hindered carbonyl groups. It is worth mentioning that organolithiums could react with aldehydes even in the absence of the aluminum reagent (Fig. 2).

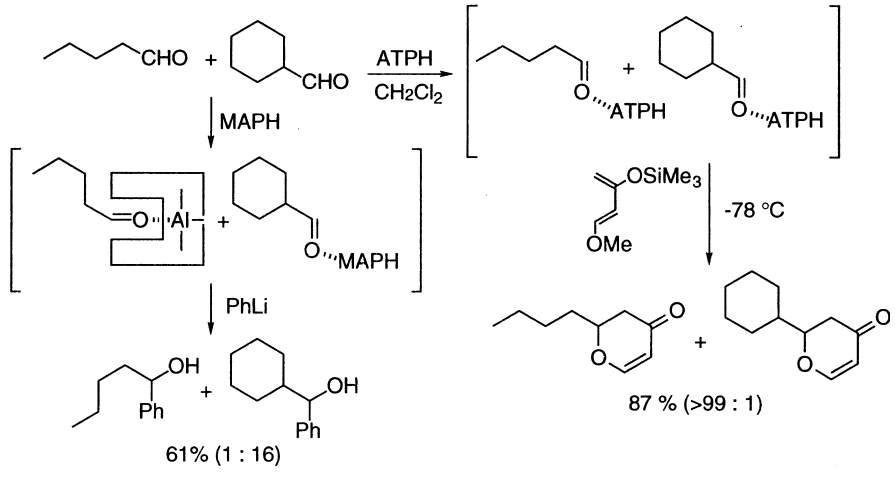

Fig. 2 Selective reaction of aldehydes using MAPH and ATPH.

CONJUGATE ADDITION TO A,B-UNSATURATED CARBONYL COMPOUNDS

Organocuprates are the most widely used reagents for Michael addition to α,β-unsaturated ketones [12], and for one of the most powerful and important carbon-carbon bond-forming reactions. ATPH can be used as a carbonyl protector upon complexation, which facilitates 1,4-addition to even α,β-unsaturated aldehydes [7] for which 1,4-addition is virtually unexplored. Complexation of cinnamaldehyde with ATPH, followed by subsequent addition of *n*-BuMgBr, gave 1,4-adduct preferentially. Under otherwise identical reaction conditions, replacing ATPH with MAD or MAPH proved both disappointing. However, organocalcium, strontium, and barium reagents enhanced 1,4-selectivity. Thus, the carbonyl carbon was sterically deactivated, while the β-carbon was electronically activated. One area where this system can be applied with a particular benefit is those proved unfruitful with organocuprates: lithium alkynides and thermally unstable lithium carbenoids can serve as Michael donors in the presence of ATPH. Michael addition of the carbenoids, followed by raising the reaction temperature allowed cyclopropanation to give a sole diastereomer (Fig. 3).

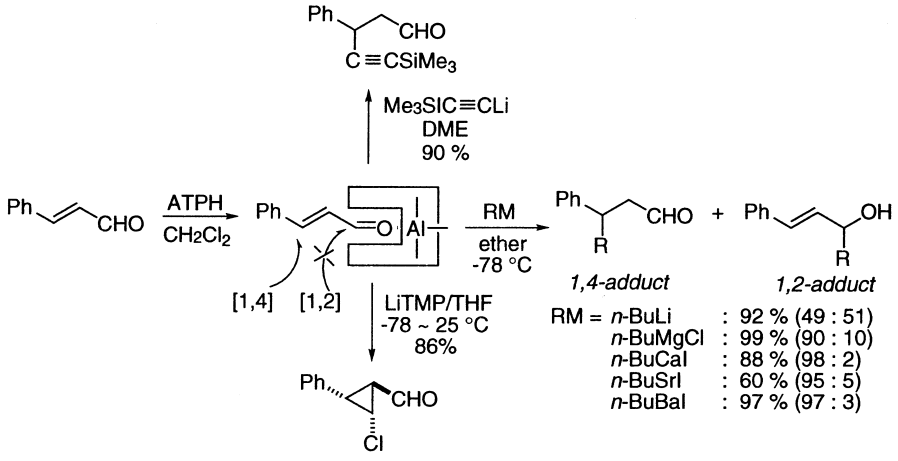

Fig. 3 Conjugate addition to the cinnamaldehyde complex.

Extention of this system to α,β-unsaturated ketones gave even more general and pronounced 1,4-selectivity (> 99:1) [13]. Various organolithiums are well suited to this ATPH/RLi system which enables the introduction of perfluoro-organo substituents at the β-positions of carbonyl functions [14]. Efficient conjugate reduction of several α,β-unsaturated carbonyl substrates was similarly realized by the combined use of ATPH and diisobutylaluminum hydride-*n*-butyllithium 'ate' complex (DIBAL-*n*-BuLi), the latter being a reducing agent [15]. Diisobutylaluminum hydride-*tert*-butyllithium (DIBAL-*t*-BuLi) in preference to DIBAL-*n*-BuLi was more efficient for the 1,4-reduction of α,β-unsaturated aldehydes (Fig. 4).

Several ketone lithium enolates and the dianions of β-dicarbonyl substrates similarly undergo highly selective 1,4-addition to various α-enones. We initially applied this observation to tandem inter- and intramolecular Michael addition, leading to a general construction of six-membered carbocycles [16]. Michael addition of the dianions derived from β-dicarbonyl compounds facilitated even another annulation: Michael addition of a dianion, followed by intramolecular aldol condensation (Fig. 4) [17].

CONJUGATE ADDITION/DEAROMATIZATION SEQUENCE FOR AROMATIC CARBONYL COMPOUNDS

The selective functionalization of an aromatic nucleus is important in synthetic organic chemistry. However, little is known about nucleophilic addition to aromatic nucleus covalently attached by a carbonyl functionality which serves as an electron-withdrawing group with weak activating capability. Accordingly, aromatic carbonyl compounds have been long believed as rather inactivated aromatics which do not allow the aromatic functonalization by the attack of nucleophiles but usually give addition at their carbonyl carbons. We recently discovered that organolithiums undergo conjugate addition to

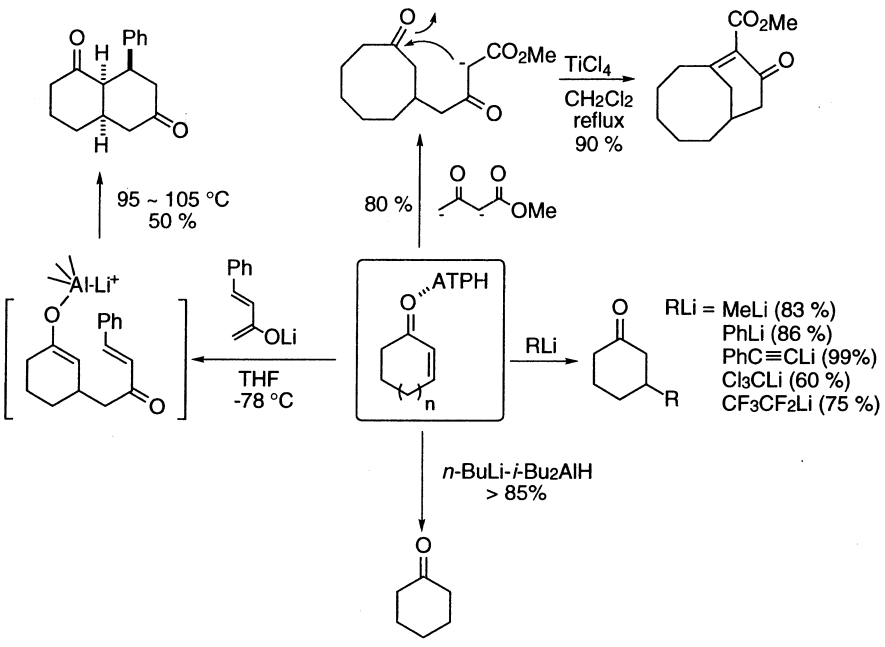

Fig. 4 Conjugate addition to the cycloalkenone complex and subsequent cyclization.

aromatic carbonyl compounds by complexation with ATPH. [18] α-Carbonylnaphthalene derivatives found to be more susceptible of 1,6-addition than carbonylphenyl derivatives, but prone to undergo 1,4-addition with reducing the size of organolithiums. This novel strategy represents a recent application to a number of nucleophiles including silyl-[19], aryl-, allyl-, and vinyllithiums [20] as well as lithium enolates of esters [21], leading to a powerful and general method for a wide range of aromatic carbonyl compounds (Fig. 5).

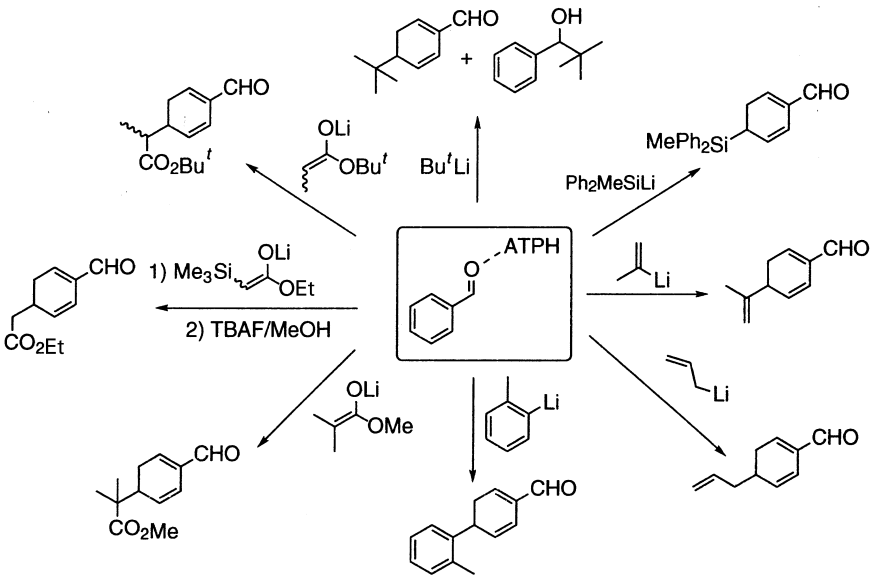

Fig. 5 Conjugate addition to the benzaldehyde complex.

SELECTIVE ALKYLATION AT THE MORE HINDERED α-CARBON OF UNSYMMETRICAL KETONES

An unsymmetrical dialkyl ketone can form two regioisomeric enolates upon deprotonation under either kinetic or thermodynamic control [22]. Ideal conditions for the kinetic control of less-substituted enolate

formation are those in which deprotonation is irreversible using lithium diisopropylamide (LDA). On the other hand, at equilibrium, the more substituted enolate is the dominant species with moderate selectivity [23]. A hitherto unknown method, i.e. the kinetically controlled generation of the more substituted enolate, was realized by the combined use of ATPH and LDA [24]. Precomplexation of ATPH with an unsymmetrical ketone, followed by sequential treatment with LDA and an alkylating agent (RX) led to predominant functionalization at the more substituted α-site (Fig. 6).

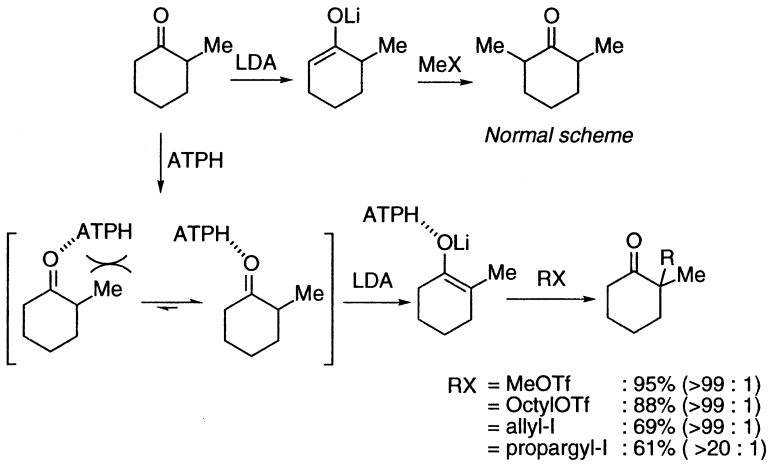

Fig. 6 Alkylation at the more hindered α-carbon using ATPH.

CONCEPTUALLY NEW DIRECTED ALDOL CONDENSATION

The control of mixed aldol condensation between two different carbonyl compounds which present several possible sites for enolization is a challenging problem for synthetic chemists. Such reactions are normally carried out by converting the carbonyl compound which is to serve as a nucleophile to an enolate. This reactive nucleophile is then allowed to react with the second carbonyl compound [25]. In the

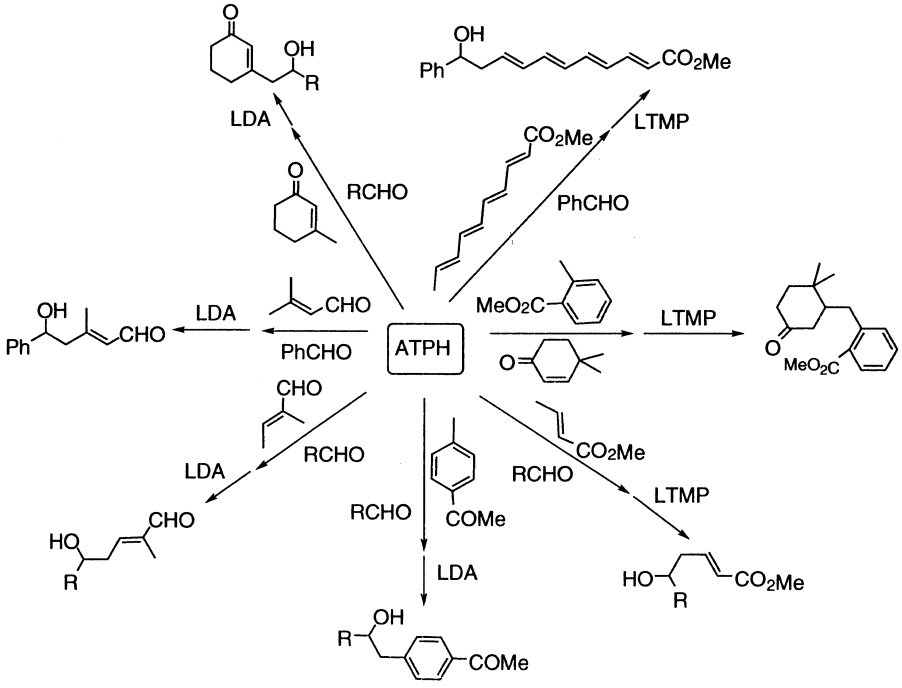

Fig. 7 Directed aldol condensation using ATPH.

presence of ATPH an entirely different strategy for combining two different carbonyl compounds are possible: (i) the two different carbonyl reactants and ATPH should be mixed together prior to treatment with a base to give effective cross-coupling, (ii) conjugated carbonyl compounds including aldehydes, ketones [26], and esters [27] all demonstrated to work as effective nucleophiles (Fig. 7), (iii) neither the α-carbon of aromatic ketones nor the α′-carbon of α,β-unsaturated ketones were directed site for deprotonation. Thus, (iv) deprotonation and ensuing alkylation are quite regioselective at an allylic terminus of given nucleophiles which serve as extended dienolates. Of particular note is the regioselective aldolization of highly conjugated esters which have several possible site for functionalization, (v) this transformation displayed high *E*-selectivity with respect to the γ-aldolization.

CLOSING REMARKS

The designer Lewis acids as exemplified by ATPH showed several unique characteristics as shown above. It should be noted that reactions using these designer Lewis acid catalysts are only exemplified part of possibilities. Thus, search for a new and practical designer Lewis acid still remains a challenge in selective organic synthesis.

ACKNOWLEDGEMENTS

We are indebted to our co-workers whose names appear in the references, with whom it has been a great pleasure to be associated. We also thank the financial support of the Ministry of Education, Science, Sports, and Culture of Japan.

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