JOC The Journal of Organic Chemistry

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Borrowing Hydrogen Methodology for Amine Synthesis under Solvent-Free Microwave Conditions

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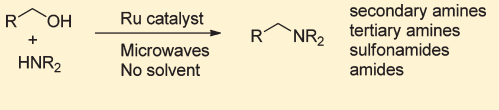
Supporting Information

ABSTRACT: Application of microwave heating to the Borrowing Hydrogen strategy to form C−N bonds from alcohols and amines is presented, removing the need for solvent and reducing the reaction times while still yielding results comparable with those using thermal heating.



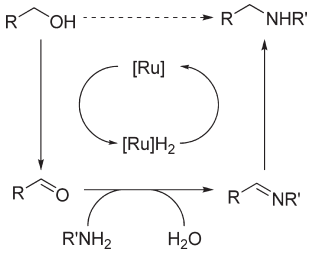
Borrowing Hydrogen methodology has been used for a wide range of coupling reactions using alcohols as nontoxic alkylating agents to form C−C and C−N bonds with a wide range of nucleophiles[1,2] producing water as the only waste product (Scheme 1). The use of these reactions is increasing due to the ease in which they can be performed and the wide range of alcohols which can be used.

Of the Borrowing Hydrogen reactions available in the literature, the formation of C−N bonds has been applied to the synthesis of several pharmaceuticals. The ease in which they can be performed, coupled with the advantages they offer over more traditional C−N bond-forming reactions (avoiding the use of toxic reagents, avoiding stoichiometric reducing agents, generating water as the only byproduct, and the selectivity to form either secondary or tertiary amines without over alkylation), makes these reactions synthetically appealing. However, the disadvantage is that typically these reactions are run at high temperatures for periods of up to 24 h, although temperatures down to 70 °C have been reported.[1n]

Grigg[3] and Watanabe[4] independently developed the first examples of C−N bond formation from alcohols, but more recent developments have led to more active catalysts and milder conditions. Beller's group used a ruthenium carbonyl cluster with bulky phosphine ligands,[5] and while Yamaguchi and co-workers have used $[Cp^*IrCl_2]_2$,[6] Kempe[7] and Marr[8] have also used iridium-based catalyst incorporating P−N ligands to achieve good results. Our own group has also been successful[9] in applying the $[Ru(p\text{-cymene})Cl_2]_2$ with diphosphines to couple a wide range of amines, sulfonamides, alcohols, and diols together.

While the reactions show a wide range of functional group tolerance,[10] the long reaction times are a disadvantage. Grigg and co-workers have addressed this problem by using solvent-free microwave heating[11] to reduce reaction times significantly, but to date, this has only been applied to C−C bond formation.[12] Using our simple ruthenium-based catalyst with a diphosphine ligand,[9] we have shown that microwave heating can also be applied to C−N bond-forming reactions of amines, amides, and sulfonamides with primary alcohols, shortening the reaction times to just a few hours.

Scheme 1. Borrowing Hydrogen Strategy for the Alkylation of Amines with Alcohols

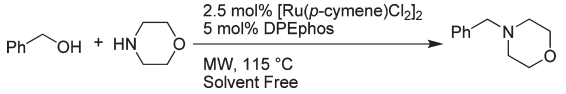


By screening a range of conditions and applying them to a model system, a range of catalysts,[13] conditions, and solvents (toluene, dioxane, DME) were tested; however, product was only observed when no solvent was present. Furthermore, better results were obtained when an excess of alcohol was used (entry 1, Table 1). Despite screening water and a range of alcohols (MeOH, IPA, ^{t}BuOH) as solvents, the reaction only proceeded efficiently in an excess of the reagent alcohol. It was then possible to reduce the excess of alcohol used to 1.6 equiv (entry 3, Table 1) without affecting the conversion. However, reducing the amount further led to a reduced conversion (entry 4, Table 1), and even on prolonged heating, no further gain in the conversion was obtained (entry 5, Table 1). With the conditions established, we were pleased to see that increasing the scale (entry 6, Table 1) in this case had no effect on the reaction.

After we established suitable reaction conditions, various secondary amines and alcohols were coupled to evaluate the reliability of the reaction (Table 2). We were pleased to see that all of the products could be isolated in high yields, comparable with thermal heating for longer periods.[9c] The use of excess amine instead of alcohol (entry 2, Table 2) was also pleasing as this meant the least expensive coupling partner, whichever it may

Received: January 5, 2011
Published: February 23, 2011

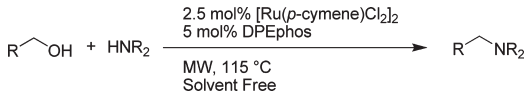
Table 1. Optimization of Conditions[a]

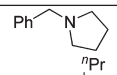
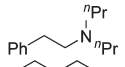
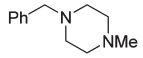
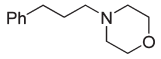
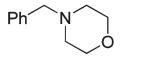


entry	equiv of alcohol	time (min)	conversion[b]
1	3	60	>99
2	2	60	>99
3	1.6	90	>99
4	1.2	90	94
5	1.2	120	94
6	1.6	90	>99[c]

[a] Reaction conditions: morpholine (1 mmol), benzyl alcohol, [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol %), DPEphos (5 mol %), 115 °C. [b] Determined by analysis of the ^{1}H NMR spectra. [c] Reaction scaled by 3 times.

Table 2. Alkylation Secondary Amines[a]



entry	product	eq. of alcohol	time (min)	yield (%)
1		1.6	90	79
2		2.0[b,c]	90	94
3		1.6	120	79
4		1.6	90	83
5		1.6	90	81

[a] Reaction conditions: amine (1 mmol), alcohol (1.6 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol %), DPEphos (5 mol %), 115 °C. [b] Equivalent of amine. [c] At 125 °C.

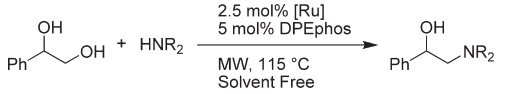
be, can be used in excess while still giving good yields. Although the reactions proceeded well, the increase in temperature (125 °C) for entry 2, Table 2, was necessary to force the reaction to completion.

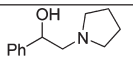
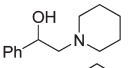
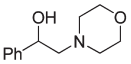
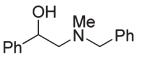
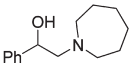
Next we wanted to determine whether microwave heating had any affect on the selectivity[5d,9c] of the reaction for primary/secondary alcohols. Morpholine was then reacted with a series of 1,2-diols; however, only diols with a benzylic secondary alcohol were active toward coupling, while the use of alkyl 1,2-diols led to the oxidation of the secondary alcohol to the ketone. This is in contrast to previously reported thermal coupling reactions, suggesting that there may be limitations to the use of microwave heating in specific cases. With the limitation of the 1,2-diol substrate evaluated, various secondary amines were screened against 1-phenyl-1,2-ethanediol[5d] (Table 3).

Again, the yields gave good results for most substrates (entries 1−3, Table 3); however, the introduction of acyclic amine (entry 4, Table 3) or a larger cyclic amine (entry 5, Table 3) led to a reduction in yield due to losses in the product isolation.

We then turned our attention to the coupling of primary amines, which under the previous conditions gave poor conversion into product. We assume this deactivation of the catalyst to be the result of the amine binding more tightly to

Table 3. Alkylation of 1,2-Diols[a]



entry	product	eq. of amine	time (min)	yield (%)
1		2.0	90	75
2		2.0	90	90
3		2.0	120	79
4		2.0	90	61
5		2.0	90	65

[a] Reaction conditions: diol (1 mmol), amine (2 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol %), DPEphos (5 mol %), 115 °C.

the catalyst under the concentrated conditions.[14] Assuming this to be the case, we increased the reaction temperature by 10 °C and were pleased to see that the reaction progressed to full conversion. With the new conditions established, a series of primary amines were coupled to evaluate the scope of the reaction (Table 4).

As expected, the results were good, with a range of alcohols and amines coupling in high yields. Even anilines (entries 1 and 2, Table 4) gave good results at lower temperatures (115 °C) as the lone pair on the nitrogen is less nucleophilic, so it will bind less tightly to the catalyst, reducing deactivation. Bulky amines (entries 3−5, Table 4) also coupled well and again gave yields comparable with thermal heating.

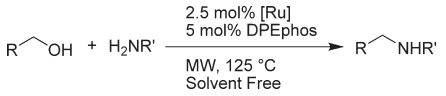
Having determined that we could monoalkylate primary amines, we wanted to see if we could dialkylate using symmetric diols.[4b,6a,9c] Again, a slight increase in temperature (135 °C) was required for the reaction to proceed. With the conditions established, a range of substrates were screened (Table 5) giving generally good yields, comparable with our previously reported results.[9c] The only exception was furfurylamine (entry 5, Table 5), which gave a lower yield, consistent with the results of thermal heating. We were also very pleased to see that, when an enantiopure amine (entry 4, Table 5) was alkylated, it did not undergo racemization.

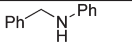
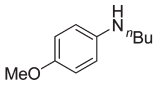
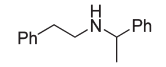
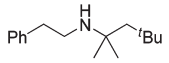
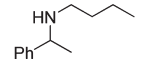
Having screened a series of different amine and alcohol couplings, we turned our attention toward the alkylation of sulfonamides.[9c,15] To allow the reaction to proceed, an increase in temperature (165 °C) was required and an increased reaction time (180 min) to drive the reaction to completion. An increased amount of alcohol was also necessary; we assume this was required to dissolve the sulfonamide. However, contrary to previous reports, the inclusion of an inorganic base to deprotonate the sulfonamide was not required. The results of the sulfonamide couplings (Table 6) were good, with high yields except for cyclopropylmethanol (entry 3, Table 6). In this case, the yield was low due to the alcohol undergoing oxidative dimerization to form the ester.

Satisfied that we could replicate the previous results and couplings, we decided to see if we could extend our catalyst's scope and alkylate primary amides in the same way. Previously, we have been unsuccessful in this area, although there

dx.doi.org/10.1021/jo102521a |*J. Org. Chem.* 2011, 76, 2328–2331

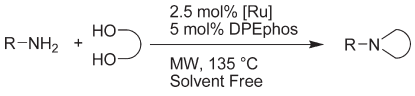
Table 4. Alkylation of Primary Amines[a]

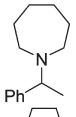
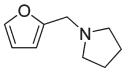


entry	product	eq. of amine	time (min)	yield (%)[b]
1		3.0	120	91[c]
2		2.1	120	73[c]
3		1.6	60	94
4		2.0	90	82
5		1.6	60	80

[a] Reaction conditions: amine (1 mmol), alcohol (1.6 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol %), DPEphos (5 mol %), 125 °C. [b] Isolated yield. [c] At 115 °C.

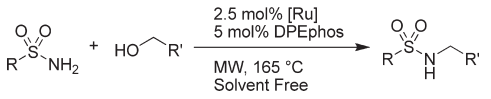
Table 5. Reaction of Amines with Diols To Form N-Heterocycles[a]

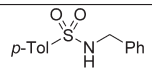
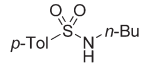
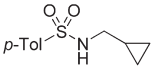
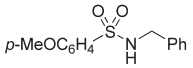
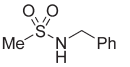


entry	product	eq. of diol	time (min)	yield (%)
1		1.6	90	88
2		1.6	90	81
3		1.6	90	77
4		1.6	90	82
5		1.6	90	54

[a] Reaction conditions: amine (1 mmol), diol (1.6 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol %), DPEphos (5 mol %), 135 °C.

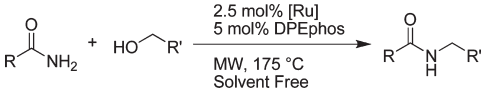
Table 6. Alkylation of Sulfonamides[a]

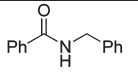
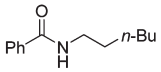
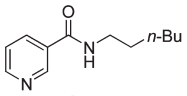
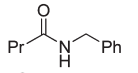
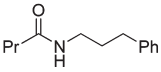


entry	product	eq. of alcohol	time (min)	yield (%)
1		3.0	120	91
2		3.0	180	96
3		3.0	180	74
4		3.0	180	91
5		3.0	180	86

[a] Reaction conditions: amine (1 mmol), alcohol (3 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol %), DPEphos (5 mol %), 165 °C.

Table 7. Alkylation of Primary Amides[a]



entry	product	eq. of alcohol	time (min)	yield (%)
1		3.0	120	66
2		3.0	120	72
3		3.0	180	54[b]
4		3.0	120	74
5		3.0	120	79

[a] Reaction conditions: amide (1 mmol), alcohol (3 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol %), DPEphos (5 mol %), 175 °C. [b] At 180 °C.

are at least three reports in the literature[16] of this being achieved, but with high reaction temperatures. By starting with the sulfonamide conditions, we quickly determined that the coupling of primary amides and alcohols was possible, although to reach full conversion, the reaction temperature had to be pushed to 175 °C. Despite the high reaction temperature, the reaction time was shorter than the coupling of sulfonamides (120 min), and once again, the coupling proceeded without the need for a base. We were then able to evaluate the coupling scope in comparison with the system reported by Yamaguchi et al.[16c]

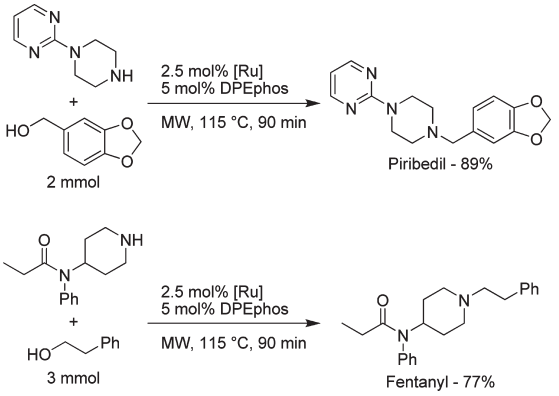
Both aromatic (entries 1 and 2, Table 7) and alkyl amides (entries 4 and 5, Table 7) were coupled with aliphatic and benzylic alcohols with reasonable yields. The coupling of alkyl amides was interesting as the yields were better than those reported by Yamaguchi, even though the reaction temperature was significantly higher. Finally, we were very pleased to isolate *N*-hexylnicotinamide in reasonable yield (entry 3, Table 7),[17] thus demonstrating that the reaction was also applicable to biologically relevant molecules.

With a range of reaction conditions established, we were keen to apply our chemistry to two pharmaceutical compounds, piribedil and fentanyl, both of which were isolated in good yield (Scheme 2).

To conclude, we have shown that the use of microwave heating can be used to carry out C−N bond formation using Borrowing Hydrogen methodology. Furthermore, that these reactions can be conducted more quickly than using thermal heating methods. Finally, we have expanded the scope of our catalyst to include the N-alkylation of primary amides as well as demonstrating that the methodology can be applied to the synthesis of biologically relevant compounds.

dx.doi.org/10.1021/jo102521a |*J. Org. Chem.* 2011, 76, 2328–2331

Scheme 2. Synthesis of Piribedil and Fentanyl[a]



[a] Reaction conditions: diol (1 mmol), amine (2 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol %), DPEphos (5 mol %), 115 °C.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of *N*-Benzylmorpholine. DPEphos (26.9 mg, 5 mol %), [Ru(*p*-cymene)Cl_2]$_2$ (15.3 mg, 2.5 mol %), benzyl alcohol (166 μL, 1.6 equiv), and morpholine (87 μL, 1 mmol) were added to a microwave vial containing a stirrer bar. The vial was then sealed before purging with N_2 for 5 min. The reaction was then heated to 115 °C for 90 min using a microwave. The crude material was then purified by silica column chromatography (3:1 petroleum ether (bp 40−60 °C)/EtOAc, R_f = 0.19) to give *N*-benzylmorpholine (144 mg, 81% yield): ^{1}H NMR δ ($CDCl_3$, 300 MHz, 25 °C) δ 7.20−7.27 (5H, m), 3.66 (4H, t, J = 4.7 Hz), 3.45 (2H, s), 2.39 (4H, t, J = 4.5 Hz); ^{13}C NMR δ ($CDCl_3$, 75.4 MHz, 25 °C) δ 137.7, 129.3, 128.3, 127.2, 67.0, 63.5, 53.6; HRMS(ESI-TOF) calcd for $C_{11}H_{16}NOH^+$ 178.1232, found 178.1229 (MH^+).

ASSOCIATED CONTENT

Supporting Information. General experimental conditions, analytical data, and ^{1}H and ^{13}C NMR data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

We thank GlaxoSmithKline, Pfizer, AstraZeneca, Novartis, and the EPSRC for providing a studentship (to A.J.A.W.) through the collaborative EPSRC-Pharma-Synthesis Programme. We also thank Christopher Tame for his support and enthusiasm.

REFERENCES

(1) (a) Grigg, R.; Lofberg, C.; Whitney, S.; Sridharan, V.; Keep, A.; Derrick, A. *Tetrahedron* **2009**, *65*, 849–864. (b) Fujita, K.; Asai, C.; Yamaguchi, T.; Hanasaka, F.; Yamaguchi, R. *Org. Lett.* **2005**, *7*, 4017–4019. (c) Iuchi, Y.; Hyotanishi, M.; Miller, B. E.; Maede, K.; Obora, Y.; Ishii, Y. *J. Org. Chem.* **2010**, *75*, 1803–1806. (d) Blank, B.; Kempe, R. *J. Am. Chem. Soc.* **2010**, *132*, 924–925. (e) Grigg, R.; Whitney, S.; Sridharan, V.; Keep, A.; Derrick, A. *Tetrahedron* **2009**, *65*, 7468–7473. (f) Whitney, S.; Grigg, R.; Derrick, A.; Keep, A. *Org. Lett.* **2007**, *9*, 3299–3302. (g) Jensen, T.; Madsen, R. *J. Org. Chem.* **2009**, *74*, 3990–3992. (h) Iuchi, Y.; Obora, Y.; Ishii, Y. *J. Am. Chem. Soc.* **2010**, *132*, 2536–2537. (i) Löfberg, C.; Grigg, R.; Keep, A.; Derrick, A.; Sridharan, V.; Kilner, C. *Chem. Commun.* **2006**, *42*, 5000–5002. (j) Pridmore, S. J.; Williams, J. M. J. *Tetrahedron Lett.* **2008**, *49*, 7413–7415. (k) Edwards, M. G.; Jazzar, R. F. R.; Paine, B. M.; Shermer, D. J.; Whittlesey, M. K.; Williams, J. M. J.; Edney, J. J. *Chem. Commun.* **2004**, *40*, 90–91. (l) Black, P. J.; Cami-Kobeci, G.; Edwards, M. G.; Slatford, P. A.; Whittlesey, M. K.; Williams, J. M. J. *Org. Biomol. Chem.* **2006**, 116–125. (m) Black, P. J.; Edwards, M. G.; Williams, J. M. J. *Eur. J. Org. Chem.* **2006**, *4*, 4367–4378. (n) Blank, B.; Michlik, S.; Kempe, R. *Chem.—Eur. J.* **2009**, *15*, 3790–3799.

(2) For a reviews on Borrowing Hydrogen, see: (a) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 1555–1575. (b) Nixon, T. D.; Whittlesey, M. K.; Williams, J. M. J. *Dalton Trans.* **2009**, *38*, 753–762. (c) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681–703.

(3) Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S.; Tongpenyai, N. *J. Chem. Soc., Chem. Commun.* **1981**, *12*, 611–612.

(4) (a) Watanabe, Y.; Tsuji, Y.; Ohsugi, Y.; Ohta, T. *J. Org. Chem.* **1984**, *49*, 3359–3363. (b) Tsuji, Y.; Huh, H.-T.; Ohsugi, Y.; Watanabe., Y. *J. Org. Chem.* **1985**, *50*, 1365–1370.

(5) (a) Tillack, A.; Hollmann, D.; Mevius, K.; Michalik, D.; Bähn, S.; Beller, M. *Eur. J. Org. Chem.* **2008**, *28*, 4745–4750. (b) Hollmann, D.; Tillack, A.; Michalik, D.; Jackstell, R.; Beller, M. *Chem. Asian J.* **2007**, *2*, 403–410. (c) Tillack, A.; Hollmann, D.; Michalik, D.; Beller, M. *Tetrahedron Lett.* **2006**, *47*, 8881–8885. (d) Bähn, S.; Tillack, A.; Imm, S.; Mevius, M.; Michalik, M.; Hollmann, D.; Neubert, L.; Beller, M. *ChemSusChem* **2009**, *2*, 551–557.

(6) (a) Fujita, K.; Fujii, T.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 3525–3538. (b) Yamaguchi, R.; Kawagoe, S.; Asai, C.; Fujita, K. *Org. Lett.* **2008**, *10*, 181–184. (c) Fujita, K.; Li, Z.; Ozeki, N.; Yamaguchi, R. *Tetrahedron Lett.* **2003**, *44*, 2687–2690. (d) Fujita, K.; Enoki, Y.; Yamaguchi, R. *Tetrahedron* **2008**, *64*, 1943–1954.

(7) (a) Blank, B.; Madalska, M.; Kempe, R. *Adv. Synth. Catal.* **2008**, *350*, 749–758. (b) Blank, B.; Michlik, S.; Kempe, R. *Adv. Synth. Catal.* **2009**, *351*, 2903–2911.

(8) Liu, S.; Rebros, M.; Stephens, G.; Marr, A. C. *Chem. Commun.* **2009**, *45*, 2308–2310.

(9) (a) Hamid, M. H. S. A.; Williams, J. M. J. *Tetrahedron Lett.* **2007**, *48*, 8263–8265. (b) Hamid, M. H. S. A.; Williams, J. M. J. *Chem. Commun.* **2007**, *43*, 725–727. (c) Hamid, M. H. S. A.; Allen, C. L.; Lamb, G. W.; Maxwell, A. C.; Maytum, H. C.; Watson, A. J. A.; Williams, J. M. J. *J. Am. Chem. Soc.* **2009**, *131*, 1766–1774.

(10) For a review on C−N Borrowing Hydrogen reactions, see: Guillena, G.; Ramón, D. J.; Yus, M. *Chem. Rev.* **2010**, *110*, 1611–1641.

(11) Microwave papers: (a) Grigg, R.; Whitney, S.; Sridharan, V.; Keep, A.; Derrick, A. *Tetrahedron* **2009**, *65*, 4375–4383. (b) Löfberg, C.; Grigg, R.; Whittaker, M. A.; Keep, A.; Derrick, A. *J. Org. Chem.* **2006**, *71*, 8023–8027.

(12) Palladium-catalyzed amine−amine coupling using Borrowing Hydrogen methodology in a microwave was reported during the preparation of this paper: Lubinu, M. C.; De Luca, L.; Giacomelli, G.; Porcheddu, A. *Chem.—Eur. J.* **2010**, *17*, 82–85.

(13) [IrCp*Cl_2]$_2$ was active under the conditions, although in our hands the combination of $Ru_3(CO)_{12}$ and tri(*o*-tolyl)phospine was not.

(14) Samec, J. S. M.; Éll, A. H.; Åberg, J. B.; Privalov, T.; Eriksson, L.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2006**, *128*, 14293–14305.

(15) Zhu, M.; Fujita, K.; Yamaguchi, R. *Org. Lett.* **2010**, *12*, 1336–1339.

(16) (a) Watanabe, Y.; Ohta, T. Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2647–2651. (b) Jenner, G. *J. Mol. Catal.* **1989**, *55*, 241–246. (c) Fujita, K.; Komatsubara, A.; Yamaguchi, R. *Tetrahedron* **2009**, *65*, 3624–3628.

(17) The reaction went to 84% conversion, and the low yield is attributed to difficulties in purification by silica column chromatography.